Total Synthesis of Bakkanes

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Abstract: A review showing the synthetic efforts toward the syntheses of bakkanes from the first total synthesis in 1973 until the middle of 2000 is presented. Approaches for constructing β-methylene-γ-butyrolactones are also reviewed.

Key words: total synthesis, natural products, bakkanes, bakkenolides, β-methylene-γ-butyrolactone

1 Introduction

Terpenes show an enormous structural variety as well as a number of remarkable biological activities.1–5 Therefore, their total syntheses have been one of the most active and challenging areas in organic chemistry.6 Among numerous types of terpenes, the relatively small class of bakkanes has been the focus of several synthetic efforts during the last years, as will be shown in this review article.

Bakkanes are sesquiterpenoids possessing a cis-fused hydridane that bears two quaternary carbons (C-5 and C-7), as shows the general skeleton in Figure 1. The stereochemistry at C-7 is not depicted because both stereoisomers are observed in the class of bakkanes. However, the isopropyl group is more frequently found in a trans relationship to the vicinal methyl groups (C-14 and C-15), which are always in a cis relationship. Most bakkanes show a β-methylene-γ-butyrolactone (Figure 1), which, albeit not present in all members of this class, can be considered the most important structural moiety of these compounds. Interestingly, only the bakkanes that show the isopropyl group (at C-7) in trans relationship to the vicinal methyl groups also possess the β-methylene-γ-butyrolactone moiety. The absolute configuration of the bakkane skeleton has been determined by chemical degradation to a known compound,7 as well as by X-ray analysis of a bakkane derivative.8 The carbon numbering was established considering that these compounds are biogenetically derived from eremophilanes,7,9 whose skeleton is also shown in Figure 1. The two above-mentioned classes usually occur at the same species as for example, in Petasites japonicus.7,10,11

Although the great majority of bakkanes was isolated on the terrestrial environment of Asia and Europe, they also occur in the Indian Ocean. Tables 1 and 2 show the bakkanes isolated until the middle of 2000, with the respective species and its location.

The simplest and most famous member of the class of bakkanes is bakkenolide-A, whose structure is shown in Table 1, entry 1. This compound was independently isolated by two Japanese groups in 1968. Curiously, each group gave a different name to the compound, based on different Japanese local names of the species. Considering the local name “bakke”, Kitahara and his co-workers12 nominated the, by then, new sesquiterpene lactone as bakkenolide-A, which is the name mainly found in the literature. On the other hand, Naya et al.7 gave the name fukinanolide to the same lactone, due to the local name “fuki”. Arbitrarily, the nomenclature of Kitahara12 will be used during this review.

Several biological activities have been attributed to sesquiterpene lactones, including some of the bakkanes shown above.13–15 Cytotoxic activity is a characteristic of

Figure 1
Luiz Fernando Silva, Jr. was born in São Paulo, Brazil, in 1971. He studied chemistry at the University of São Paulo, where he received his B.Sc. in 1993. In 1994, he joined the group of Professor H. M. C. Ferraz at the University of São Paulo, as a graduate student and received his Ph.D. in 1999. During his thesis, he was involved in the study of the ring contraction reaction promoted by thallium(III) salts. Then, he worked one year as a FAPESP postdoctoral research associate with Professor H. M. C. Ferraz and looking for an academic position. His research interests include the total synthesis of natural products and the development of thallium(III) promoted reactions. Besides chemistry, he also enjoys sport climbing and high mountain climbing.
several bakkanes (bakkenolide-A, bakkenolide-D, -G, -H and -Uc). In addition, bakkenolide-A shows anti-feedant activity and inhibits larval growth. Bakkenolide-G and -H (Table 2, entry 6) inhibit the activity against platelet activation factor. Bakkenolide-G is also a specific PAF-receptor antagonist, for example, as an antiplatelet aggregatory agent. Finally, Bakkenolide-Uc (Table 2, entry 6) shows inhibitory activity against arachidonic acid and collagen.

In this review article, a survey of the synthetic approaches toward the total synthesis of bakkanes published until the middle of 2000 will be given. Before presenting each of the several total syntheses of bakkanes, studies concerning the construction of \( \beta \)-methylene-\( \gamma \)-butyrolactones will be discussed.

**Table 2** Bakkanes Isolated Until Mid 2000

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bakkane Species</th>
<th>Species (Location)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Petasites japonicus</td>
<td>(Japan)</td>
</tr>
<tr>
<td></td>
<td>Homofukinolide:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( R_1 = R_2 = OA_{ng} )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dihydrofukinolide:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( R_1 = OA_{c}, R_2 = OC )</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Homogynolide-A</td>
<td>(Czechoslovakia, Switzerland)</td>
</tr>
<tr>
<td></td>
<td>( R_1 = OA_{ng}, R_2 = H )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Homogynolide-B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( R_1 = H, R_2 = OTigl )</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Homogynolide alpine</td>
<td>(Switzerland)</td>
</tr>
<tr>
<td>4</td>
<td>Coelogorgia palmo-sa</td>
<td>(Indian Ocean)</td>
</tr>
<tr>
<td>5</td>
<td>Senecio auricula</td>
<td>(Spain)</td>
</tr>
<tr>
<td>6</td>
<td>Petasites formosanus</td>
<td>(Taiwan)</td>
</tr>
<tr>
<td>7</td>
<td>Bakkenolides D to III</td>
<td>(Taiwan)</td>
</tr>
</tbody>
</table>

For structures of OA_{ng}, OTigl, O-i-Val and O-i-Val, see Figure 2.

For \( R_1 \) and \( R_2 \), see Table 3.

**Table 3** Bakkenolides Isolated from *Petasites formosanus*

<table>
<thead>
<tr>
<th>Bakkenolide</th>
<th>( R_1 )</th>
<th>( R_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Db</td>
<td>(R)-cis-</td>
<td>OAC</td>
</tr>
<tr>
<td></td>
<td>OCOCH=CHSOMe</td>
<td></td>
</tr>
<tr>
<td>Dc</td>
<td>(S)-cis-</td>
<td>OAC</td>
</tr>
<tr>
<td></td>
<td>OCOCH=CHSOMe</td>
<td></td>
</tr>
<tr>
<td>Dd</td>
<td>OAC</td>
<td>cis-</td>
</tr>
<tr>
<td></td>
<td>OCOCH=CHSMe</td>
<td></td>
</tr>
<tr>
<td>De</td>
<td>OAC</td>
<td>(S)-trans-</td>
</tr>
<tr>
<td></td>
<td>OCOCH=CHSOMe</td>
<td></td>
</tr>
<tr>
<td>Df</td>
<td>OAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(S)-trans- OCOCH=CHSOMe</td>
<td></td>
</tr>
<tr>
<td>Dg</td>
<td>OAC</td>
<td>(R)-cis-</td>
</tr>
<tr>
<td></td>
<td>OCOCH=CHSOMe</td>
<td></td>
</tr>
<tr>
<td>Dh</td>
<td>OAC</td>
<td>(S)-cis-</td>
</tr>
<tr>
<td></td>
<td>OCOCH=CHSOMe</td>
<td></td>
</tr>
<tr>
<td>Fa</td>
<td>OA_{ng}</td>
<td>O-i-Val</td>
</tr>
<tr>
<td>Fb</td>
<td>O-i-Val</td>
<td>OA_{ng}</td>
</tr>
<tr>
<td>G</td>
<td>OA_{c}</td>
<td>O-i-Val</td>
</tr>
<tr>
<td>H</td>
<td>O-i-Bu</td>
<td>O-i-Bu</td>
</tr>
<tr>
<td>I</td>
<td>H</td>
<td>O-i-Bu</td>
</tr>
<tr>
<td>J</td>
<td>H</td>
<td>O-i-Val</td>
</tr>
<tr>
<td>K</td>
<td>O-i-Bu</td>
<td>OA_{ng}</td>
</tr>
<tr>
<td>L</td>
<td>OA_{c}</td>
<td>OA_{c}</td>
</tr>
<tr>
<td>M</td>
<td>OCOCH(Me)CH_{2}Me</td>
<td>O-i-Bu</td>
</tr>
<tr>
<td>Na</td>
<td>O-i-Val</td>
<td>O-i-Bu</td>
</tr>
<tr>
<td>Nb</td>
<td>O-i-Bu</td>
<td>O-i-Val</td>
</tr>
<tr>
<td>O</td>
<td>OCOCH(Me)CH_{2}Me</td>
<td>O-i-Val</td>
</tr>
<tr>
<td>P</td>
<td>OCOCH(Me)CH_{2}Me</td>
<td>OA_{ng}</td>
</tr>
<tr>
<td>Q</td>
<td>O-i-Val</td>
<td>O-i-Val</td>
</tr>
<tr>
<td>R</td>
<td>OH</td>
<td>OA_{ng}</td>
</tr>
<tr>
<td>S</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>T</td>
<td>(R)-cis-</td>
<td>O-i-Val</td>
</tr>
<tr>
<td></td>
<td>OCOCH=CHSOMe</td>
<td></td>
</tr>
<tr>
<td>Ua</td>
<td>OH</td>
<td>O-i-Bu</td>
</tr>
<tr>
<td>Ub</td>
<td>O-i-Bu</td>
<td>OH</td>
</tr>
<tr>
<td>Uc</td>
<td>H</td>
<td>O-i-Bu</td>
</tr>
</tbody>
</table>
Although \(\beta\)-methylene-\(\gamma\)-butyrolactones are not so vastly found in the nature as their isomeric \(\alpha\)-methylene-\(\gamma\)-butyrolactones,\(^{46-48}\) several approaches have been reported for synthesizing compounds bearing this moiety. In the following paragraphs, studies concerning the construction of \(\beta\)-methylene-\(\gamma\)-butyrolactones will be described. However, the methodologies used in the total syntheses of bakkanes will be shown in the context of the synthesis where the corresponding studies were applied, in the next item.

2.1 \(\beta\)-Methylene-\(\gamma\)-butyrolactones

Some protocols have been reported for preparing simple \(\beta\)-methylene-\(\gamma\)-butyrolactones from either open chain starting materials or alicyclic compounds. Starting from non-cyclic materials, Bertrand et al.\(^{49,50}\) described that the addition of organozinc compounds to alkynes leads, after work-up in aqueous medium, to the desired lactones in reasonable yields. A representative example is shown in Scheme 1.

In case of an alicyclic starting material, Haslouin and Rouessac\(^{51}\) described that the anhydride 2, prepared from cyclopentadiene and itaconic anhydride (1), can be regioselectively reduced to lactone 3, which gave the methylene lactone 4 by retro Diels-Alder reaction, as outlined in Scheme 2. Recently, another paper described the use of the same anhydride as starting material for the preparation of the \(\beta\)-methylene-\(\gamma\)-butyrolactone.\(^{52}\) Thus, the enzyme-mediated ring opening of itaconic anhydride (1), followed by reduction of the acid moiety of 5, yielded the hydroxy ester 6. Treatment of 6 with acid led to the expected lactone 4, as shown in Scheme 3.
which is responsible for the formation of the cyclopropane. Acidic ring cleavage of 8 gave the unsaturated aldehyde 9, which was transformed into the β-methylene-γ-butyrolactone 12 in a three-step sequence.

Two other approaches have also a cyclopropane derivative as intermediate for the preparation of spiro-β-methylene-γ-butyrolactone, as outlined in Schemes 4 and 6. Wenkert et al.\textsuperscript{55} have described that the copper-catalyzed reaction of the enol ether 14 and dimethyl diazomalonate (13) gave the cyclopropane ester 15, which was reduced to the corresponding diol. The cyclopropane diol 16 furnished the spiro-hemiketal 17, which gave the desired lactone after Collins oxidation (Scheme 5). In 1979, Inoue et al.\textsuperscript{56} reported that the cyclopropane 19 can be directly transformed into the spiro-lactone 12, when treated with carbon dioxide under high pressure in the presence of a palladium(0) catalyst, albeit the yield of this reaction was only modest (Scheme 6).

A compound possessing a three-membered ring was also an important intermediate in two other approaches. However, in these cases an oxirane was used instead of a cyclopropane. The first approach\textsuperscript{57,58} is shown in Scheme 7. Thus, epoxidation of the unsaturated ester 22, prepared in two steps from methyl cyclopentanecarboxylate, gave the oxirane 23. Hydrolysis of the ester function, followed by intramolecular opening of the epoxide, yielded the hydroxy lactone 24, whose dehydration furnished a 2:1 mixture of the isomeric spiro-lactones 12 and 20, respectively.

Cobaloxime I (29) can be an interesting tool for constructing spiro-lactones, as reported by Okabe and Tada\textsuperscript{60} in 1982. Thus, cyclopentanecarboxaldehyde was brominated and acetylated in a single step, leading to 27 in excellent yield. Reductive cyclization promoted by 29 gave 28, whose deprotection and oxidation afforded the desired lactone 12. The structure of 29 as well as the sequence of the above-mentioned reactions can be seen in Scheme 9. Mitsuhashi and co-workers\textsuperscript{17} have synthesized spiro-lactones from steroids. Knoevenagel reaction of the cholestanone (30) with diethyl malonate gave the diester 31, of which the diastereomeric ciano-esters 32 and 33 were obtained by cyanide addition in 45% and 25% yield,

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**Scheme 4**

Reagents and Conditions: (a) Ph$_3$P=CH(Me)CO$_2$Et; (b) LiAlH$_4$, Et$_2$O; (c) DHP; (d) MeLi, LiI, CHCl$_3$(OMe); (e) H$_2$; (f) AgNO$_3$, NaOH; (g) NBS, CCl$_4$; (h) Ag$_2$O, CCl$_4$

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**Scheme 5**

Reagents and Conditions: (a) (MeO)$_3$P, CuI, hexane, reflux; (b) LiAlH$_4$, Et$_2$O, r.t., 8 h; (c) 5% aqueous H$_2$SO$_4$, THF, reflux; (d) CrO$_3$, pyridine, CH$_2$Cl$_2$

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**Scheme 6**

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**Scheme 7**

Reagents and Conditions: (a) i) LDA, THF; ii) acetone; (b) SOCl$_2$, pyridine, benzene; (c) MCPBA, CH$_2$Cl$_2$; (d) i) 20% aqueous NaOH, MeOH, reflux; ii) HCl; (e) SOCl$_2$, pyridine, benzene

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**Scheme 8**

Reagents and Conditions: (a) i) LDA, HMPA, THF, –78 °C; ii) Br(CH$_2$)$_4$Br; (b) LDA, HMPA, THF, –78 °C; (c) MCPBA, CH$_2$Cl$_2$, 30 °C; (d) Li$_3$PO$_4$, 180 °C

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respectively. After separation, these compounds were transformed into the spiro-lactones 36 and 35, respectively in a four-step sequence as shown in Scheme 10. Altenbach and Soicke\(^61\) have shown that allenes are also suitable starting materials for the preparation of\(^97\)-spiro-\(^87\)-methylene-\(^103\)-butyrolactones (Scheme 11). Thus, the allenic sulphoxide 37 was successively alkylated with sodium malonate and methyl iodide, giving the unsaturated diester 38 in 40% yield over two steps. Allylic rearrangement of the sulphoxide 38, promoted by trimethoxyphosphine, furnished the allylic alcohol 39, which spontaneously lactonized to the desired butyrolactone 40.

3 Total Syntheses of Bakkanes

3.1 Strategies used in the Total Syntheses of Bakkanes

Although more than fifty bakkanes have been isolated (see Tables 1 and 2), only five of them—bakkenolide-A, homogynolide-A, homogynolide-B, palmosalide-C and 9-acetoxyfukinanolide—have been synthesized to date. Analyzing these syntheses, three different strategies can be recognized. In the most popular strategy, a six-membered ring starting material was transformed into a properly functionalized hydrindane, from which the spiro-lactone moiety and, consequently, the desired bakkane were formed (Strategy A). The second approach was similar to the first one, except that a hydrindane system was prepared by the ring contraction of a decalin compound (Strategy B). In the third and more convergent strategy, a Diels-Alder reaction was used for constructing the whole bicyclic bakkane system in a single step, followed by simple functional group transformations allowing the formation of the lactone moiety (Strategy C). In the next items, the total syntheses of each of the mentioned targets will be discussed and the advantages as well as drawbacks of each strategy will become clear.

3.2 Syntheses of Bakkenolide-A

Six syntheses of bakkenolide-A, which has the structure shown in Table 1, entry 1, have been accomplished.\(^62\)–\(^68\) Three of them were achieved using the above-mentioned Strategy A,\(^62,63,66,67\) two using Strategy B,\(^64,65\) and one using Strategy C.\(^68\) In the following paragraphs the syntheses will be presented according to the strategies used.

3.2.1 Evans’ Synthesis

The first synthetically available bakkane was bakkenolide-A, described by Evans et al. in 1973.\(^62,63\) The starting material was 2,3-dimethylcyclohexanone, which was transformed in six steps into the hydrindene 43, based upon the procedure described by Piers,\(^69\) as outlined in Scheme 12. Catalytic hydrogenation of 43 furnished only the desired cis-fused compound 44, which was alkylated with isopropenyl lithium, affording the epimeric alkenol 45 in 64% yield over two steps. After treatment with phos-
phorous tribromide, these alkenol furnished an unstable rearranged allylic bromide, which was immediately reacted with the sodium salt of p-toluenesulfonfonyl-S-methylcarbazate, leading to the carbazate 46.

The construction of the required quaternary center at C-7 was performed by a [2,3]-sigmatropic rearrangement\textsuperscript{63,70} of 46, which gave the dithioester 47. Remarkably, the bond reorganization occurred only across the convex face of the cis-fused hydrindane and therefore in a highly diastereoselective fashion. The formation of the β-methylene-γ-butyrolactone was realized after two more steps. Thus, treatment of 47 with an aqueous mixture of mercuric oxide and mercuric dichloride afforded the thioester 48, which, after allylic oxidation promoted by selenious acid, gave bakkenolide-A. Therefore, the total synthesis of bakkenolide-A was accomplished in 13 steps from 2,3-dimethylcyclohexanone, considering the stereoselective synthesis could be adapted to give (+)-bakkenolide-A.

3.2.2 Greene’s Syntheses

In 1985, Greene and his co-workers\textsuperscript{66} published a racemic total synthesis of bakkenolide-A, which was the first of several total syntheses of bakkanes accomplished by these investigators. In this racemic synthesis of bakkenolide-A, the mentioned research group employed a strategy that was further used for synthesizing other bakkanes, as will be shown in the following paragraphs. Three reactions play an important role in their general approach, as exemplified in the retrosynthesis of bakkenolide-A, shown in Scheme 13. Moreover, as 1,6-dimethylcyclohexene can be prepared enantiomerically pure\textsuperscript{67} (see Scheme 17), Evans’ synthesis could be adapted to give (+)-bakkenolide-A.

Following the retrosynthetic analysis, the preparation of 52 would be achieved by cleavage of the α,α-dichlorocyclobutanone 49, followed by functional group transformations (Scheme 14).\textsuperscript{73–75} Such a cleavage occurs in a three-step one pot procedure: first, formation of the enolate of the α,α-dichlorocyclobutanone by treatment with butyl lithium; second, trapping of this enolate, as its enol acetate, by addition of acetic anhydride; finally, sodium metaperiodate-ruthenium dioxide-promoted oxidation to

Scheme 13 Reagents and Conditions: (a) CCl\textsubscript{3}COCl, Zn-Cu, POCl\textsubscript{3}; (b) CH\textsubscript{2}N\textsubscript{2}; (c) Zn, AcOH

Scheme 14
the desired dicarboxylic acid. In Table 5, representative examples for previously performed total syntheses are shown.

Table 5  Cleavage of Cyclobutanones

<table>
<thead>
<tr>
<th>α,α-Dichlorocyclobutanone</th>
<th>Succinic Acid</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCClOCl</td>
<td>CO₂H</td>
<td>78</td>
</tr>
<tr>
<td>ClCClOCl</td>
<td>CO₂H</td>
<td>75</td>
</tr>
<tr>
<td>ClCClOCl</td>
<td>CO₂H</td>
<td>93</td>
</tr>
</tbody>
</table>

In the last step of the retrosynthetic analysis, cycloaddition reaction of dichloroketene and 1,6-dimethylcyclohexene would give the cyclobutanone 49, following the functional group transformations, generated the diiodide 52 in 62% yield over three steps. Dialkylation of 52 with the lactone synthon 51, using lithium bis(trimethylsilyl)amide, gave 50 as a 3:1 mixture of epimers at C-7. Deprotection and lactonization were achieved by treatment with aqueous hydrofluoric acid, leading to the desired target together with 7-epi-bakkenolide-A. Although it had been possible to separate bakkenolide-A from its epimer by crystallization, the formation of the latter compound constitutes the disadvantage of Greene’s approach to the synthesis of racemic bakkenolide-A, as well as to the total synthesis of other bakkanes (see Schemes 17 and 27).

Table 4 β-Methylene-γ-butyrolactones by Greene’s Methodology

<table>
<thead>
<tr>
<th>RX, R'X</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me, Me</td>
<td>69</td>
</tr>
<tr>
<td>MeCCH</td>
<td>81</td>
</tr>
<tr>
<td>CH₂=CHBr, CH₃OCH₂Cl</td>
<td>49</td>
</tr>
<tr>
<td>Br(CH₂)₂Br</td>
<td>49</td>
</tr>
<tr>
<td>Br(CH₂)Br</td>
<td>72</td>
</tr>
<tr>
<td>Br(CH₂)Br</td>
<td>44</td>
</tr>
</tbody>
</table>

Scheme 16  Reagents and Conditions: (a) CCl₃COCl, Zn-Cu, POCl₃; (b) i) BuLi; ii) Ac₂O; iii) RuO₂, NaIO₄; (c) LiAlH₄, THF; (d) TMSI; (e) (Me₃Si)₂NLi, 51; (f) HF, CH₃CN

Using the same route as shown in Scheme 16, Greene and his co-workers accomplished the first asymmetric synthesis of (+)-bakkenolide-A. This work was also the first asymmetric synthesis of any bakkan. The enantiomerically pure 1,6-dimethylcyclohexene was synthesized in five steps from 2-methylcyclohexanone, as described in Scheme 17. Thus, the preparation of the α,β-unsaturated ketone 54 was performed, via 2-chloro-2-methylcyclohexanone, in 49% yield. The ketone 54 was asymmetrically reduced yielding the corresponding alcohol. This alcohol was then transformed into the N-phenylcarbamate 55, which reacted with lithium dimethylcopper to the desired enantiomerically pure (S)-1,6-dimethylcyclohexene. Scheme 17 also shows how the mentioned cyclohexene was transformed in six steps into (+)-bakkenolide-A, as discussed previously (vide supra).

3.2.3 Hayashi’s Synthesis

In the same year Evans’s synthesis was published, Hayashi et al. described a route to bakkenolide-A employing the already mentioned Strategy B. As the starting material was fukinone, which is a natural eremophilane sesquiterpene, this sequence constitutes a biomimetic route to bakkenolide-A. Thus, epoxidation of fukinone, followed by base-mediated rearrangement of the resulting
oxirane 56, transformed the bicyclo[4,4,0]nonane of fukinone into a cis-hydrindane 57, together with significant amounts of two other undesired hydrindane products (58 and 59), as shown in Scheme 18. It is noteworthy that the rearrangement of other eremophilane-type compounds to hydrindanes has also been reported.7,30,77,78 A double bond was then established by treatment of the hydroxy ester 57 with thionyl chloride. Selenium(IV) dioxide mediated allylic oxidation of 60 afforded bakkenolide-A in 3% yield, together with 57% of the aldehyde 61, which was transformed into the target molecule by reduction.

3.2.4 Petragnani’s Synthesis

In 1984, Petragnani and Silva65 have accomplished a formal total synthesis of bakkenolide-A. The chosen starting material was 2,3-dimethylcyclohexanone, as in the synthesis of Evans et al.52,63 However, in the approach of Petragnani, the starting monocyclic ketone was transformed into an octalone, whereas a hydrindenone was prepared by Evans, as described in Scheme 12. The sequence studied by the authors is shown in Scheme 19. The octalone 62 was prepared in two steps from 2,3-dimethylcyclohexanone, using standard procedures. The enolate of 62 reacted with ethyl formate, giving a hydroxymethylene derivative 63, which furnished 64 after catalytic hydrogenation under basic conditions. The latter compound gave the α-diazoketone 65, whose Wolf rearrangement led to the ring contraction product 66. Formylation reaction, followed by treatment with methyl lithium, allowed the preparation of the diol 67, in 64% yield over two steps. Oxidation of this diol afforded a hydroxy-acid, which was treated with diazomethane giving the hydroxy-ester 57. Dehydration of the alcohol 57 was performed with thionyl chloride, leading to the unsaturated ester 60. It is important to note that 57 and 60 are also intermediates in the biomimetic synthesis performed by Hayashi et al.64 (see Scheme 18). Therefore, a formal total synthesis of bakkenolide-A was accomplished from...
2,3-dimethylcyclohexanone, using an interesting Wolf rearrangement to construct a required functionalized hydrindane.

The main drawback in the synthesis of Petragnani and Silva is the elevated number of functional group manipulations required for the preparation of the hydrindane. It has to be mentioned that the authors attempted a shorter route to the hydrindane. However, the ring contraction of 68 promoted by H₂O₂/SeO₂ gave the desired acid 69, together with its regioisomer 70, as shown in Scheme 20.

Scheme 20

3.2.5 Back’s Synthesis

Recently, Back and Payne²⁸ published an ambitious and novel approach (Strategy C) to the synthesis of bakkenolide-A. In their route, intramolecular Diels-Alder reaction of a functionalized triene led to a hydrindane bearing the required functional groups for a straightforward construction of the lactone moiety, achieving therefore bakkenolide-A.

Three building blocks were necessary for the preparation of the required triene. Thus, the bromide 71 was prepared in three steps from tiglyc acid, using standard protocols. Ethyl 4-chloroacetoacetate furnished 72 by treatment with sodium hydride and benzyl alcohol. Finally, base-catalyzed ring-opening of dihydropyran, followed by reaction with phosphorous tribromide gave the bromodione 73, in good yield. The preparation of these building blocks as well as the following steps of the synthesis are shown in Scheme 21. The β-keto ester 72 was then sequentially alkylated with 71 and 73, leading to the triene 74 in very good overall yield. The key step – a Diels-Alder reaction – furnished the unsaturated hydrindane 75 as a mixture of diastereomers. Reaction of this mixture with H₂, in the presence of a palladium catalyst, allowed the hydrogenation of the double bond, the hydrogenolysis of the benzyl group and, consequently, the cyclization to the keto-lactone 76. Finally, the exocyclic double bond was formed by a Wittig reaction, leading to bakkenolide-A together with three other epimers (77, 78 and 79). In summary, Back and Payne showed a highly convergent approach to the synthesis of bakkenolide-A, although the key Diels-Alder reaction has furnished all four possible, and not easily separable C-7 and C-10 epimers.

Back et al.⁷⁹,⁸⁰ have also investigated another approach for the preparation of compounds possessing the bakke skeleton, using an intermolecular Diels-Alder reaction instead of the intramolecular version shown above. The spiro-lactone 82, prepared as shown in Scheme 22, gave a mixture of three diastereomers (84, 85 and 86) after Diels-Alder reaction under high pressure conditions, as outlined in Scheme 23. Two of these compounds (84 and 86) show the wrong configuration at the C-7 stereo-center. It is noteworthy that several other Lewis acids as well as low pressure conditions were tried. The Diels-Alder reaction of the β-methylene lactone 83, which was obtained after elimination/oxidation of the selenide 82 (Scheme 22), gave similar results.
Several transformations were performed with 84, 85 and 86, as depicted in Scheme 24. The lactone 84 was separated from 85 and 86 and transformed into the 3,6-dioxo-7-epi-bakkenolide-A (87) in a five-step sequence. The isomers 85 and 86, which could not be separated from each other, were oxidized to the corresponding β-methylene-lactones 88 and 89, whose separation was easily achieved. 88 and 89 furnished the ketones 90 and 92, respectively, using the same sequence of reactions used in the preparation of 87. Epimerization of these ketones (90 and 92) with DBU furnished 3,6-dioxobakkenolide-A (91) and its C-7 epimer 87, thus circulating the wrong configuration at C-4 obtained in the Diels-Alder reaction.

A second approach, performing an intermolecular Diels-Alder reaction, was tested by Back and co-workers. The reaction of 2-methyl-2-cyclopenten-1-one with piperylene gave the unsaturated ketone 93, which furnished 94 after hydroboration, protection, acylation and selenylation, as depicted in Scheme 25. Radical cyclization furnished the lactone 95, which also shows the wrong configuration at C-7. The C-4 configuration was corrected using similar functional group transformations as for ketone 87 (see Scheme 24).

Another research group attempted to use a Diels-Alder reaction in the synthesis of bakkanes. In their studies toward the synthesis of bakkanes and eremophilanes, Brocksom and Constantino investigated the feasibility of using a Diels-Alder reaction for constructing functionalized cyclohexenes, which would be potential intermediates in the synthesis of the mentioned target compounds. However, the key reaction of cis-piperylene (96) with citraconic anhydride occurred with poor selectivity, leading to the desired product 97 in only 3% yield, as shown in Scheme 26. Reactions using other dienes, anhydrides or different experimental conditions were also investigated by these authors.

**Scheme 23**

**Scheme 24** Reagents and Conditions: (a) NaIO₄, H₂O, THF, r.t.; (b) MCPBA, CH₂Cl₂, r.t.; (c) Ph₃P, I₂, CH₂Cl₂, r.t.; (d) n-Bu₃SnH, benzene; (e) PDC, CH₂Cl₂, r.t.; (f) DBU, CH₂Cl₂

**Scheme 25** Reagents and Conditions: (a) piperylene; (b) BH₃, THF, r.t., 15 min; (c) TBSCl, imidazole, DMF; (d) LDA, allyl cyanofumarate, THF; (e) NaH, THF, PhSeCl; (f) benzene, hv, 20 min; (g) AcOH, H₂O, THF, r.t., 48 h; (h) NaO₂, H₂O, MeOH, r.t., 28 h; (i) PDC, CH₂Cl₂; (j) DBU, CH₂Cl₂

**Scheme 26**

3.3 Syntheses of Homogynolide-A

Apart from bakkenolide-A, the bakkane that received more attention from the synthetic chemists was homogynolide-A, which has the structure shown in Table 2, entry 2. Curiously, there are more asymmetric syntheses known for (-)-homogynolide-A than for (+)-bakkenolide-A. It seems that the presence of the ester group at C-2 in homogynolide-A facilitates the selection of a suitable enantio-merically pure starting material. In the following para-
of the carbonyl group would allow the appropriate configuration at C-2. Thus, base-catalyzed cycloalkylation of \(103\) with the lactone synthon \(51\) led, after cleavage of the enol ether, to the \(\beta\)-methylene-\(\gamma\)-butyrolactones \(104\) and \(105\) in a 1:3 ratio and in 38% yield over two steps. Finally, reduction of purified \(105\) using a hindered hydride (Li-Al(Or-Bu)_3H) allowed the formation of the alcohol with the proper relative configuration in 83% yield. The last step was the formation of the ester by reaction with angelic acid. Therefore, the first racemic total synthesis of homogynolide-A was accomplished in eighteen steps from benzoquinone.

Greene and his group\(^{84}\) also achieved the first asymmetric total synthesis of \((-\)-homogynolide-A, as shown in Scheme 28. The strategy was similar to the racemic approach. However, the preparation of the protected alcohol (intermediate \(99\)) was performed in seven steps, whereas in the racemic approach only four steps were necessary. Thus, the chosen starting material – the monoterpene \((S)-(+)\)-carvone – was treated with lithium dimethylcopper and the resulting enolate was trapped, affording an enol phosphate. Selective ozonolysis, followed by Criegee rearrangement, allowed the formation of the required protected alcohol, in form of its acetate \(106\). Cleavage of the enol phosphate with lithium in methylamine led to a cyclohexene derivative, which after a two-step sequence – oxidation and reduction – produced an inversion in the configuration at the C-2 center, resulting in a cyclohexenol. This alcohol was then protected as the benzyl ether, delivering the required enantiomerically pure starting material \(99\). The next steps were performed as in the racemic synthesis (see Scheme 27), affording \((-\)-homogynolide-A after a total of 22 steps from \((S)-(+)\)-carvone.

graphs the four – three total and one formal – syntheses of homogynolide-A will be discussed.

3.3.1 Greene’s Syntheses

Using the general strategy described in Scheme 14, Greene and his group\(^{85}\) accomplished the first total synthesis of homogynolide-A, as shown in Scheme 27. The unsaturated ketone \(98\), prepared in two steps from benzoquinone, was reduced to the corresponding alcohol, which was then protected giving \(99\). Cycloaddition reaction of \(99\) with dichloroketene led to the \(\alpha,\alpha\)-dichlorocyclobutanone \(100\). Cleavage of the enol acetate of cyclobutanone \(100\) gave, after in situ esterification, the diester \(101\). The latter was reduced to a diol, further transformed into its ditriflate and then into the diiodide \(102\), the cleavage of the benzyl ether also occurring in the last step of this sequence. Oxidation of the hydroxyl function, followed by protection of the carbonyl group, furnished compound \(103\). The oxidation of the hydroxyl group, which must be regenerated at the end of the synthesis, has two reasons, as explained by the authors. First, the stereoselectivity in the formation of the quaternary carbon C-7 would increase during the cycloalkylation reaction. Second, the reduction

\[ \text{Scheme 27 Reagents and Conditions: (a) LiAlH}_4, \text{THF}, -78^\circ\text{C}; (b) NaH, BuCl, Bu,Ni (cat), THF, reflux; (c) CCl}_4, \text{POCl}_3, \text{Zn-Cu, Et}_2\text{O, reflux; (d) Me}_2\text{CuLi, Et}_2\text{O, -50}^\circ\text{C then Ac}_2\text{O, -50 to -20}^\circ\text{C; (e) O}_2, \text{CH}_2\text{Cl}_2, \text{MeOH}, -78^\circ\text{C then Me}_2\text{S, -78 to 20}^\circ\text{C; (f) aq NaOH, MeI, HMPA, 20}^\circ\text{C; (g) LiAlH}_4, \text{THF, 20}^\circ\text{C; (h) Tf}_2\text{O, 2,6-di-t-butylpyridine, CH}_2\text{Cl}_2, -30^\circ\text{C; (i) Bu}_2\text{NI, toluene, 20}^\circ\text{C; (j) TMSI, CH}_2\text{Cl}_2, -78^\circ\text{C then Ac}_2\text{O, 20}^\circ\text{C; (k) PCC, CH}_2\text{Cl}_2; (l) (H}_3\text{C})_2\text{C(CH}_2\text{OH})_2, \text{BF}_3\cdot\text{Et}_2\text{O, MeOH, 0}^\circ\text{C; (m) (H}_3\text{C})_2\text{C}(-\text{Bu})_3\text{H, THF, 0}^\circ\text{C; (n) HOAc, Et}_3\text{N, Cl}_2\text{C}_6\text{H}_2\text{COCl, THF, 20}^\circ\text{C} \]

of the carboxyl group would allow the appropriate configuration at C-2. Thus, base-catalyzed cycloalkylation of \(103\) with the lactone synthon \(51\) led, after cleavage of the enol ether, to the \(\beta\)-methylene-\(\gamma\)-butyrolactones \(104\) and \(105\) in a 1:3 ratio and in 38% yield over two steps. Finally, reduction of purified \(105\) using a hindered hydride (Li-Al(Or-Bu)_3H) allowed the formation of the alcohol with the proper relative configuration in 83% yield. The last step was the formation of the ester by reaction with angelic acid. Therefore, the first racemic total synthesis of homogynolide-A was accomplished in eighteen steps from benzoquinone.

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\[ \text{Scheme 28 Reagents and Conditions: (a) i) Me}_2\text{CuLi; ii) Et}_2\text{O}(\text{OCl})_2; (b) ozonolysis; (c) p-NO}_2\text{C}_6\text{H}_4\text{COCl, CH}_2\text{Cl}_2, \text{heating; (d) Li, MeNH}_2; (e) H}_2\text{CrO}_4, \text{Et}_2\text{O/H}_2\text{O; (f) LiAlH}_4; (g) NaH, BuCl; (h) CCl}_4, \text{POCl}_3, \text{Zn-Cu, Et}_2\text{O, reflux; (i) Me}_2\text{CuLi, Et}_2\text{O, then Ac}_2\text{O; (j) O}_2, \text{CH}_2\text{Cl}_2, \text{MeOH, then Me}_2\text{S, -78 to 20}^\circ\text{C; (k) aq NaOH, MeI, HMPA; (l) LiAlH}_4, \text{THF; (m) TMSI, CH}_2\text{Cl}_2; (n) Bu}_2\text{NI, toluene; (o) TMSI, CH}_2\text{Cl}_2; (p) TMSI, CH}_2\text{Cl}_2; (q) PCC, CH}_2\text{Cl}_2; (r) Me}_2\text{C}(-\text{Bu})_3\text{H, THF, 0}^\circ\text{C; (s) LiAl(O-r-Bu)_3H, THF, 0}^\circ\text{C; (t) angelic acid, Et}_3\text{N, Cl}_2\text{C}_6\text{H}_2\text{COCl, THF} \]
3.3.2 Mori’s Synthesis

In 1995, two more approaches to synthesize (-)-homogynolide-A have been published. Mori et al. reported a total synthesis of the mentioned bakkane, whereas Srikrishna et al. accomplished a formal synthesis of (-)-homogynolide-A.

The synthesis of Mori refers to the already mentioned Strategy B, where a decalinic compound is transformed into a functionalized hydrindane by a ring contraction reaction. The decalinic compound was prepared according to the following procedure (Scheme 29). The enantiomerically pure alcohol 108, prepared by Baker’s yeast reduction of the corresponding diketone, was protected as the corresponding ethoxy ethyl (EE) ether and then alkylated using LDA/MeLi, giving 109 in excellent yield. Reduction of the corresponding enol triflate of the ketone 109 allowed to establish the required double bond. Deprotection and oxidation led to the ketone 110 in 79% yield over four steps. A Grignard reaction in presence of cerium(III) chloride gave a 3:4 mixture of compounds 111 and 112 in modest yield. The key step in the synthesis was an oxy-Cope rearrangement, which was best performed using potassium hydride as base and toluene as solvent, giving the desired product 113 in 27% yield. Protection of the ketone and ozonolysis of the double bond, followed by intramolecular aldol reaction, gave the hydrindane 114. Catalytic hydrogenation of the latter gave a methyl ketone, whose alkylation furnished the dicarbonylic compound 115, obtaining the quaternary center at C-7 in a highly stereo-controlled reaction. Lactonization was carried out via epoxidation of the enol ether of 115, affording the ketolactone 116. Four more steps led to the desired target. Thus, Wittig reaction, deprotection of the ketone at C-2, reduction using a hindered hydride, and incorporation of the ester group utilizing the lactone 117 (Figure 3) afforded (-)-homogynolide-A. In summary, Mori et al. accomplished an asymmetric synthesis of the mentioned bakkane, using a strategy somewhat different from the more usual approaches. An oxy-Cope rearrangement was applied in the preparation of a decalin framework, which was transformed into a functionalized hydrindane. Finally, the β-methylene-γ-butyrolactone moiety was obtained.

![Figure 3](image_url)

3.3.3 Srikrishna’s Synthesis

Srikrishna and his group have been investigating the development of appropriate methods for the synthesis of natural bakkanes as well as of several compounds possessing this skeleton. Their studies culminated in the total synthesis of homogynolide-A and homogynolide-B. In the following paragraphs, the studies concerning the construction of model compounds will be discussed before presenting the total synthesis of homogynolide-A.

A four-step annulation process for the transformation of allylic alcohols into hydrindenes which are potentially useful intermediates for the synthesis of bakkanes, has been reported by Srikrishna et al., as exemplified in Scheme 30. Thus, 2-cyclohexen-1-ol was transformed into the bromo ketal 118, by treatment with 2-methoxypropene and NBS. The 5-exo-trig radical cyclization of the following paragraphs, the studies concerning the construction of model compounds will be discussed before presenting the total synthesis of homogynolide-A.
118 afforded the ketal 119, which gave the diketone 120 after Jones oxidation. Finally, aldol ring closure allowed the formation of the desired hydrindenone 121.

Srikrishna and his group92 have also reported a new approach for the synthesis of α-methylene-γ-spiro-butyrolactones. In this methodology a 5-exo-dig radical cyclization is the key step, as shown in the representative example of Scheme 31. Cyclopentanone was transformed into the bromo-ketal 123 in a two-step sequence. The key radical cyclization of the latter compound furnished the unsaturated ketal 124, similarly to the bromo ketal 118 in the Scheme 30. Routine deprotection/oxidation gave the desired lactone 12.

Based on the success of the radical cyclizations described above (Schemes 30 and 31), Srikrishna and his group started to investigate the synthesis of more challenging targets. As depicted in Scheme 32, an asymmetric total synthesis of (−)-7-epi-bakkenolide-A was performed in twelve steps from the commercially available R-(−)-carvone.92 The first step was the methyl addition, followed by trapping the resulting enolate with allyl bromide, leading to 125. The latter compound was oxidized with palladium chloride under Wacker conditions to furnish the methyl ketones 126 and 127 in 13% and 70% yield, respectively. After purification, 127 was submitted to Criegee rearrangement, giving the acetoxyl dione 128 and the trione 129 as a 4.3:1 mixture. After separation, 128 was transformed into hydridaneone 44 using standard protocols. The hydridaneone 44 is also an intermediate in the synthesis of Evans.62,63 Applying the radical cyclization protocol to the hydridaneone 44 via the bromo ketal derivative 131, the total synthesis of (−)-7-epi-bakkenolide-A was accomplished (Scheme 31). It is noteworthy that the radical cyclization led to the lactone with the non-natural configuration at C-7, similarly to the result obtained by Back80 (see Scheme 25).

Initially, Srikrishna and his group93 supposed that the radical cyclization of 131 would lead to the stereoisomer with the right relative configuration at C-7. Ultimately, however, the authors found that the non-natural compound-7-epi-bakkenolide-was obtained.92 For the synthesis of homogyonolide-A, performed by Srikrishna86,87-carvone was used as starting material, like in Greene’s asymmetric synthesis. However, instead of the more expensive S-enantiomer, Srikrishna chose the R-enantiomer.

The first reaction in the formal total synthesis invented by Srikrishna and his group was the treatment of (R)-(−)-carvone with an excess of diazomethane, giving the pyrazoline 133, which furnished the dimethyl α,β-unsaturated ketone 134 after heating.84 as outlined in Scheme 33. The latter ketone was reduced with lithium in liquid ammonia, following by trapping the enolate with allyl bromide. Intramolecular aldol reaction furnished a α,β-unsaturated hydridenone, which after catalytic hydrogenation gave the ketone 135. The required oxy group at C-2 was incorporated according to the following procedure. Hydrobromination, followed by elimination using DBU allowed the isomerization of the double bond, giving the compound 136 in 80% yield. Ozonolysis of the double bond gave a ketone, which was protected as its dioxyline derivative 137. Using the radical-mediated cyclization strategy, previously described in Scheme 33, the spiro-cyclic system 139 was constructed via the bromo alkyne 138. Finally, deprotection of the carbonyl group and oxidation of the resulting keto-lactol gave a 1:3.5 mixture of the ketones 105 and 104, where only the minor compound shows the appropriate configuration at C-7. As the ketone 105 had
already been transformed into (-)-homogynolide-A by Greene et al.84 (see Scheme 28), Srikrishna et al.86 accomplished a formal total synthesis of the mentioned bakkane. Srikrishna et al.87,89 also reported an alternative and potentially useful synthesis of a compound similar to 137.

### 3.4 Syntheses of Homogynolide-B

Two research groups, namely those of Greene96 and Srikrishna,87,89 have reported racemic syntheses of the bakkane homogynolide-B. Homogynolide-B, whose structure is depicted in Table 2, entry 2, differs from bakkenolide-A by an ester group at C-3.

#### 3.4.1 Greene’s Synthesis

Greene and his co-workers96 have also achieved the first racemic total synthesis of homogynolide-B in fourteen steps, using the general strategy already described (see Scheme 14). Thus, the ketal 140 (Scheme 34), prepared from 2,3-dimethylanisole in three steps, was chosen as the starting material. This ketal bears the necessary functionalities, namely a double bond (required for the cycloaddition reaction), the two vicinal methyl groups, and an oxygenated carbon (protected as a dioxolane derivative), which will allow the incorporation of the ester group at C-3. Thus, 140 was transformed into a cyclobutanone (via a cycloaddition reaction), whose enol acetate was cleaved by ozonolyzis, esterified and reduced, leading to the diol 141. Its transformation into the diiodide 142 led also to deprotection of the carbonyl group, which was then protected. The intermediate 142 was dialkyated with the lactone synthon 51, giving the lactone 143 after deprotection and hydrolysis of the silyl ether. Reduction with sodium borohydride furnished a 2:3 mixture of the alcohols 144 and 145. The major and undesired isomer 145 was recycled to the ketone 143 by oxidation. The last step of the synthesis was the esterification of the hydroxyl group of 144, leading to the racemic target molecule.

#### 3.4.2 Srikrishna’s Synthesis

Srikrishna et al.,87,89 in their formal synthesis of homogynolide-B, used Hagemann’s ester (146) as starting material, which was transformed into the hydridanone 151 in seven steps, as shown in Scheme 35. Thus, alkylation, protection (with isomerisation of the double bond), and reduction using standard protocols, converted 146 into 147. Claisen rearrangement of 147 gave an epimeric mixture of 148, which was transformed into the diketones 149.
3.5 Synthesis of Palmosalide-C

Palmosalide-C, whose structure is shown in Table 2, entry 4, shows different characteristics compared to other synthesized bakkanes. It was found in the Indian Ocean, whereas all the others are from terrestrial environments. Moreover, its quaternary center at C-7 has the opposite absolute configuration. Finally, instead of the β-methylene group, it shows a challenging epoxide group at the spiro-lactone.

3.5.1 Greene’s Synthesis

The only synthesis reported so far was achieved by Greene et al.97 in 1993. As outlined in Scheme 37, this synthesis was accomplished in sixteen steps from 1,6-dimethylcyclohexene, which is the same starting material in other Greene’s bakkanes syntheses (see Schemes 16 and 17). The mentioned substrate was transformed into the diester 154, as previously described (see Schemes 16). The required double bond was formed via selenoxide elimination, leading to the unsaturated diester 155. Reduction to a diol, followed by reaction with EtSO₂Cl, gave the chlorosulphonic ester 156. Dialkylation of 156 with methyl t-butyl malonate allowed the construction of the hydrindene 157, which gave keto-lactone 158 by alkylation with methyl cyanoformate followed by lactonization. Grignard addition followed by elimination gave the lactones 159 and 160, in a 1:1.5 ratio. The major and undesired lactone 160 was recycled to 158 by ozonolysis, whereas 159 was transformed into the chloride 161. Epoxidation of 161 gave a 1:2:1 mixture of the desired (162) and undesired (163) epoxides, respectively. Finally, after purification and reduction of the C-Cl bond, 162 led to racemic palmosalide-C.

3.6 Syntheses of 9-Acetoxyfukinanolide

In contrast to the other synthesized bakkanes, 9-acetoxyfukinanolide possesses an ester group at the five-membered carbocycle, as shown in Table 1, entry 6. Two syntheses of this molecule have been reported to date, and will be described in the following paragraphs.

3.6.1 Greene’s Syntheses

Greene et al.98 have successfully achieved the total synthesis of 9-acetoxyfukinanolide in a short route, as depicted in Scheme 38. During this synthesis, Greene and his co-workers adopted a strategy different from his aforementioned syntheses. The butanone formed in the cycloaddition reaction led to a hydrindane by a ring expansion reaction, whereas in the other syntheses the butanone had been cleaved (see Schemes 16, 17, 27, 28, 34 and 37). Thus, 1,6-dimethylcyclohexene gave the butanone 164 after cycloaddition reaction and treatment with zinc in acetic acid. Regioselective ring expansion of 164 was carried out using ethyl diazoacetate in the presence of antimony pentachloride, giving the keto-ester 165.
After trans-esterification of the ethyl ester 165 to its corresponding propargyl ester, radical cyclization promoted by manganese(II) acetate originated the spiro-lactone 166, which shows the wrong configuration at C-7. Reduction of the ketone 166 to the alcohol 167 was best performed using samarium(II) iodide. The last step of the synthesis was the successive treatment of 167 with TBAB and acetyl chloride, giving the bakkane 9-acetoxyfukinanolide. Notably, in presence of the former reagent the authors achieved the epimerization of C-7 to the natural configuration of 9-acetoxyfukinanolide. Such a transformation was explained by a retroaldol-aldol reaction.

Subsequently, Greene et al. 99 also performed the asymmetric total synthesis of 9-acetoxyfukinanolide using the same route as shown in Scheme 38. The starting material (S)-1,6-dimethylcyclohexene was prepared as described in Scheme 17.

4 Conclusion

This review has attempted to summarize the studies concerning the total synthesis of bakkanes, including methodologies toward the synthesis of the important moiety β-methylene-γ-butyrolactone. Fifteen total syntheses of five members of the class of bakkanes have been successfully accomplished during the last three decades. In many of the reported syntheses, the low stereo-control in the formation of some stereo-centers shows that important issues remain for achieving more efficient bakkane syntheses. The general approach developed by Greene and his co-workers, which culminated in eight total syntheses, deserves to be highlighted.

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References

(3) For examples of diterpenoids, see: Hanson, J. R. Nat. Prod. Rep. 2000, 17, 165.