Synthesis of Enantiomerically and Diastereomerically Pure 4-Hydroxy-1,2-alkadienyl Carbamates and Their Application in a Modified Nazarov Cyclization Towards Chiral Cyclopentenones

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Abstract: The addition of racemic titanated alkynyl N,N-diisopropylcarbamates onto enantiopure α-dibenzylamino- or α-silyloxy-alkanals affords two (out of four possible) diastereomeric, phenyl-2-cyclopenten-1-ones (stereohomogeneous, highly substituted 5-alkylidene-2,3-dialkyl-4-phenyl-2-cyclopenten-1-ones (Z,R)-25 and (E,R)-26.

Key words: diastereoselectivity, allenes, Nazarov reactions, carbamates, cyclizations, cyclopentenones

Optically active allenes are useful building blocks for the synthesis of various complex compounds. Especially, there is a growing demand for the asymmetric synthesis of α-hydroxyallenes due to their broad applicability for example in the formation of 2,5-dihydrofurans.

A method for the synthesis of racemic 4-hydroxyallenyl carbamates has been developed in our research group (Scheme 1). After α-deprotonation of 2-butylnyl N,N-diisopropylcarbamate (1a) with n-butyllithium, transmetalation with Ti(O-Pr)₃ and subsequent addition onto aldehydes or ketones, the racemic 4-hydroxyallenyl carbamates syn-2 were isolated with good yields and excellent diastereomeric ratios.

Further investigations of some optically active secondary 2-alkynyl carbamates revealed that the formation of alkynyl carbinols proceeds with a high degree of chirality transfer.

A few years ago, we reported a useful entry into enantiopure syn-4-hydroxy-1,2-alkadienyl carbamates syn-6 by a (−)-sparteine-mediated lithiation of alkynyl carbamates 1. Based on our method, transmetalation of chiral lithium compound 3 with C(Ti(O-Pr))₃ leads under inversion of configuration to organotitanium compound (R)-4, which was converted with various aldehydes via transition state 5 into a range of substituted allenyl carbamates syn-6 (Scheme 2). A selective crystallization of the (1S)-configured lithiated carbamate (S)-3 is the crucial step in this synthesis and, so far, this methodology is limited to the carbamates bearing the trimethylsilyl group (1b) and tert-butyl group (1c).

For expanding the scope of this protocol, we investigated another methodology for the preparation of enantiomerically pure 4-hydroxyallenes syn,syn-11, syn,anti-12 and syn,syn-13, syn,anti-14 (Scheme 3). Transformation of the 2-alkynyl carbamate 1a,b with BuLi proceeds in the presence of TMEDA to form the racemic lithium compound 7a,b. Transmetalation with Ti(Oi-Pr)₄ and subsequent γ-carbonyl addition with chiral amino aldehydes (S)-9 or (S)-10 took place with high γ-regioselectivity and high syn-diastereoselectivity to afford almost a 1:1 mix-
tures of enantiomerically pure diastereomers 11, 12 and 13, 14, respectively, in good yields (Table 1). The diastereomeric 4-hydroxyallyl carbamates 11, 12 and 13, 14 are easily separated by column chromatography to give enantiomerically and diastereomerically pure products 11, 12 and 13, 14, respectively.

We proved the enantiomeric excess of 95% in 5 examples (syn,syn-11a; syn,syn-11c; syn,anti-12a; syn,anti-12b and syn,anti-12c). The optical purity of the allenes corresponds with that of the α-chiral aldehydes. Since we used in all cases optically pure aldehydes it is concluded that also the other products syn,syn-11b; syn,syn-11d; syn,syn-11e; syn,syn-11f; syn,syn-13a; syn,anti-12d; syn,anti-12e; syn,anti-12f and syn,anti-14a (see Table 1) have 95% ee. Aldehydes (S)-9a–c were prepared in three steps from naturally occurring amino acids by a modified Reetz procedure. Benzylolation of the amino acid and reduction with LiAlH4 formed the corresponding alcohol in good yield (58–79%). Instead of standard Swern oxidation, we employed the sulfur trioxide–pyridine/DMSO modification, resulting in an excellent yield (95–100%) of the desired analytically pure aldehyde (S)-9. Aldehyde (S)-10 was prepared in two steps starting from (−)-methyl lactate, which has been silylated with tert-butyldiphenylsilyl chloride and reduced with DIBALH to the corresponding aldehyde (S)-10.

A similar route to prepare 5-dibenzylamino-4-hydroxy-1,2-dienes was reported by Reißig et al. They used titanated alkynyl carbamate to form diastereoselectively α-adducts.

It is noticeable that the yields of the syn,syn-allenes 11, 13 are often (entries 2, 3, 4, 6, 7 in Table 1) lower than the yields of the syn,anti-allenes 12, 14. A reason might be the formation of a mismatched pair situation during the addition of the (S)-configured aldehyde to the (1R)-configured titanated alkynyl carbamate (R)-8.

To prove this assumption, the titanated alkynyl carbamate 8a was reacted with 1.3 equiv aldehyde (S)-9a under standard conditions. The reaction was stopped after 20 min by the addition of MeOH. After separation of the two diastereomers, syn,syn-allene 11a was furnished in 8% yield whereas syn,anti-allene 12a was isolated in 27% yield. In another reaction, 0.5 equiv of aldehyde (S)-9a were used instead of the usual amount of 1.3 equiv of aldehyde. After 3 hours we found 5% of syn,syn-allene 11a and 22% of syn,anti-allene 12a.

Both results show the effect of the kinetic resolution in this γ-carbonyl addition with preference to the formation of 1,4-syn, 4,5-anti-allenes 12 and 14, respectively.

### Table 1 γ-Carbonyl Addition of 2-Alkynyl Carbamate 1 with α-Chiral Aldehydes (S)-9 or (S)-10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>R¹</th>
<th>Aldehyde</th>
<th>R²</th>
<th>syn,syn-Allene</th>
<th>Yield (%)</th>
<th>syn,anti-Allene</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
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<td>1b</td>
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<td>Ph</td>
<td>11b</td>
<td>40</td>
<td>12b</td>
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<tr>
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<td>1a</td>
<td>Me</td>
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<td>i-Pr</td>
<td>11c</td>
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<td>H</td>
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<td>7</td>
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<td>SiMe₃</td>
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<td>H</td>
<td>13a</td>
<td>28</td>
<td>14a</td>
<td>44</td>
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</table>

Nevertheless, it is possible to increase the yield of the syn,syn-allenes 11b and 11d up to 47% (Scheme 4) almost without the formation of their corresponding syn,anti-allenes 12b,d (Table 2) by using the (−)-spartheine-mediated lithiation of alkynyl carbamate 1b which was mentioned previously. This methodology should also be applicable to the selective synthesis of syn,syn-allenes 11f and 13a.

Scheme 4  Selective synthesis of syn,syn-allenes by the (−)-spartheine-mediated lithiation of alkynyl carbamate 1b: a) BuLi, (−)-spartheine, pentane, −78 °C; b) ClTi(O-i-Pr)3, −78 °C; c) aldehyde (S)-9, −78 °C; (11b: R2 = Ph; 11d: R2 = i-Pr).

The results show that this methodology has a wide range of applicability. But there are also some limitations especially if carbamate 1a (R1 = Me) is used. We investigated two differently substituted pairs of diastereomers 15a,b and 16a,b, which we were not able to separate by simple flash column chromatography on silica gel (Figure 1).

Figure 1  Two pairs of inseparable diastereomers 15a,b and 16a,b

In order to prove the relative and absolute configuration of the allenes, we prepared silyl compound 18 in 50% yield over two steps starting from syn,syn-allene 11c (Scheme 5). After O-protection with tert-butylidimethylsilyl triflate and 2,6-lutidine in CH2Cl2, the prepared silyl ether 17 was deprotonated with BuLi in toluene at −78 °C to give a configurationally stable lithium species, which was then trapped with trimethylsilyl chloride to form compound 18.

Scheme 5  Preparation of silyl compound 18: a) TBDMSOTf, 2,6-lutidine, CH2Cl2, 0 °C, b) 30 min, r.t.; b) i) BuLi, TMEDA, toluene, −78 °C, 1.5 h, 90 min, ii) Me3SiCl, −78 °C, 3 h.

Figure 2 shows the crystal structure13 of silyl compound 18. Since we used enantiomerically pure (S)-configured aldehyde (S)-9b, we can determine the absolute configuration of the stereocenters of C-4 and the allenic residue to aR,4S,5S. The absolute configuration of the allene 11c is therefore aS,4S,5S.

Figure 2  Crystal structure of (aR,4S,5S)-4-(tert-butylidimethylsilyl-oxy)-5-dibenzylamino-3,7-dimethyl-1-trimethylsilyl-1,2-octadienyl N,N-diisopropylcarbamate (18).13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>syn,syn-Allene</th>
<th>Yield (%)</th>
<th>syn,anti-Allene</th>
<th>Yield (%)</th>
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<tbody>
<tr>
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<td>11b</td>
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<td>12b</td>
<td>1.0</td>
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<td>11d</td>
<td>47</td>
<td>12d</td>
<td>1.6</td>
<td>97.3</td>
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</table>

Table 2  Selective Synthesis of syn,syn-Allenes by the (−)-Spartheine-Mediated Lithiation of Alkynyl Carbamate 1b
In view of the ease with which optically pure 4-hydroxyallenyl carbamates can be prepared from racemic alkynyl carbamates by γ-addition of the titanated alkyne to α-chiral aldehydes, this methodology offers an attractive route to appropriate precursors for consecutive reactions. Like in a brick-box manner it is possible to prepare a variety of enantiopure allenes just by exchanging substituents in the alkyne and by choosing suitable α-chiral aldehydes.

For an application of these chiral allenyl carbamates, we focused our attention to the work reported by Tius.14,15 He reported a modified Nazarov cyclization that makes use of allenyl ethers for the preparation of diverse, highly functionalized cyclopentenones. In cooperation with Tius, we reported recently an unusual method for the conversion of allenyl carbamates by a modified Nazarov cyclization that makes use of racemic alkynyl carbamates to chiral aldehydes. This methodology offers an attractive route to appropriate precursors for consecutive reactions. In view of the ease with which optically pure 4-hydroxyallenyl carbamates can be prepared from racemic alkynyl carbamates by γ-addition of the titanated alkyne to α-chiral aldehydes, this methodology offers an attractive route to appropriate precursors for consecutive reactions. Like in a brick-box manner it is possible to prepare a variety of enantiopure allenes just by exchanging substituents in the alkyne and by choosing suitable α-chiral aldehydes.

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The next stage of our investigations was to explore how chiral 4-hydroxylallenyl carbamates, respectively, reacted in this cyclization reaction. First, we prepared silyl ethers 23 and 24 as appropriate precursors by simple O-protection of the corresponding allenes with tert-butylimethylsilyl triflate and 2,6-lutidine in CH2Cl2 within 1 h. After deprotonation of the protected allenes 23 and 24 (1.5 equiv), respectively, with BuLi (1.3 equiv), addition of enone 20a (R1 = Me, R2 = Ph) (1.0 equiv) gave cyclopentenone (Z,R)-25 in 33% yield and (E,R)-26 in 25% yield, respectively (Scheme 7).17

The configuration of the double bond was determined by NOE experiment. The absolute configuration of C-4 is deduced from the mechanism (Scheme 8).16

After α-lithiation of compound 23, a configurationally stable Li-carbanion 27 was formed due to the strong chelating features of the carbamoyl function. This lithium compound 27 was then trapped with the enone 20a to form the lithium alcoloholate 28. Schultz–Fademrecht did not observe any preference for either of the two enantiotopic faces of the enone.15 After 1 hour at −78 °C, the addition was complete and the reaction mixture was allowed to warm up to r.t. During this time, the carbamoyl group migrated to form lithium 1,2-dienolate 29. In this compound, the bisallylic tertiary carbamoyloxy group acts as a leaving group during the cycloalkylation. The to-
polopoly of the ring closure is determined by the stereocchemistry of the carbon that bears the leaving group. The reaction proceeds in an anti $S_{E}$ substitution fashion in the allylic system with respect to the carbamoyloxy group. Therefore, the conrotatory ring closure reaction proceeds stereospecifically to form stereohomogeneous cyclopentenone (Z,R)-25.

Until now, we have not been able to find also the expected E-configured cyclopentenone, although other unidentified compounds could be isolated by column chromatography. The elicitation of the reason for the absence of E-configured products is the next focus of our research.

In conclusion, the methods outlined before allow for the preparation of chiral and highly substituted cyclopentenones in which the substituents at the stereogenic side chain and at the cyclopentenone core structure can be easily modified. Cyclopentenones are important intermediates in natural product synthesis, because their structure occurs in number of biologically active compounds such as prostaglandins, pyrethroids, and steroids.

All moisture-sensitive reactions were carried out under an atmosphere of argon in flame-dried glassware sealed by rubber septa. The solvents (toluene, $CH_{2}Cl_{2}$) were dried according to standard procedures and distilled prior to use. Additions of chemicals were performed by using disposable plastic syringes. Solvents for chromatography (Et$_2$O, n-pentane, EtOAc) were distilled prior to use. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh) at a pressure of about 1.5 bar. For analytic TLC, Merck plastic sheets (60 F 254 silica gel) were used. Visualization was accomplished with UV light and vanillin solution or permanganate.

The solvents (toluene, $CH_{2}Cl_{2}$) were dried according to standard procedures and distilled prior to use. The water bath temperature was maintained below 40 °C. 1H and 13C NMR spectra were recorded on a Bruker ARX 300 or AMX 400 spectrometer. Chemical shifts are given in ppm (ppm).

4-Hydroxy-1,2-alkadienyl Carbamates in Nazarov Cyclization to Cyclopentenones

(aS,4S,5S)-[5-(Dibenzy lamino)-4-hydroxy-3-methyl-6-phenyl-1,2-hexadienyl] N,N-Diisopropylcarbamate (11a) and (aR,4R,5S)-[5-(Dibenzy lamino)-4-hydroxy-3-methyl-6-phenyl-1,2-hexadienyl] N,N-Diisopropylcarbamate (12a)

SPECIAL TOPIC

4-Hydroxy-1,2-alkadienyl Carbamates in Nazarov Cyclization to Cyclopentenones

Yield: 11% (1.85 mmol; 38%); light yellow solid; mp 93.5 °C (EtO; $R_f$ 0.65 for $n$-pentane, $R_f$ 1:3).

Yield: 994 mg (1.85 mmol; 38%); light yellow solid; mp 93.5 °C (EtO; $R_f$ 0.65 for $n$-pentane, 1:3). The reaction was stopped by addition of MeOH (0.5 mL/mmol) at −78 °C and addition of sat. aq

NH$_4$Cl (3 mL/mmol) at 0 °C. The mixture was diluted with EtOAc (20 mL/mmol) and the organic layer was vigorously washed with sat. aq KNa tartrate solution (20 mL/mmol). The aq phase was extracted with EtOAc (3 × 20 mL/mmol) and the combined organic phases were dried (MgSO$_4$). The solvent was evaporated and the residue was purified by column chromatography (silica gel; Et$_2$O–n-pentane, 1:5 → 1:3 → 1:1).

4-Hydroxy-1,2-alkadienyl Carbamates in Nazarov Cyclization to Cyclopentenones

(aS,4S,5S)-[5-(Dibenzy lamino)-4-hydroxy-3-methyl-6-phenyl-1,2-hexadienyl] N,N-Diisopropylcarbamate (11a) and (aR,4R,5S)-[5-(Dibenzy lamino)-4-hydroxy-3-methyl-6-phenyl-1,2-hexadienyl] N,N-Diisopropylcarbamate (12a)

**Compound 12b**

Yield: 2.33 g (3.98 mmol; 42%); colorless solid; mp 113 °C (Et2O); Rf 0.17 (EtO−n-pentane, 1:3); [α]D+ 134.8 (c 1.00, CHCl3).

1H NMR (400 MHz, CDCl3): δ = 0.04 [s, 9 H, Si(CH3)3], 1.14 (br s, 12 H, 2′H), 2.56 (br s, 1 H, OH), 2.82–3.01 (m, 2 H, 3′J = 14.3, 4′J = 7.7 Hz, 6–H1), 3.15 (dd, 1 H, 1J = 1.5, 2′J = 14.3, 4′J = 7.7 Hz, 6–H1), 3.58–3.82 (m, 4 H, 3′J = 14.3, 2′J = 7.7 Hz, (PhCH2)3N), 4.81–4.91 (m, 1 H, 1J = 1.5, 2J = 2.5 Hz, 4–H1), 7.01–7.36 (m, 15 H, 5Hphenyl), 7.60 (d, 1 H, 1J = 2.5 Hz, 1–H1).

13C NMR (100 MHz, CDCl3): δ = 1.11 [Si(CH3)3], 20.5 (C-2′), 30.1 (C-6), 46.2 (C-1′), 54.3 (PhCH2)3N, 62.5 (C-3′), 70.1 (C-4), 114.9 (C-1′), 121.3 (C-3′), 125.7, 126.4, 127.9, 128.0, 128.4, 129.9, 140.2, 140.6 (Cphenyl), 153.3 (NC≡O), 196.8 (C-2′).

Anal. Calcd for C36H48N2O3Si (584.86): C, 73.93; H, 8.27; N, 4.79. Found: C, 74.06; H, 8.01; N, 4.53.

**Compound 11c**

Yield: 887 mg (1.61 mmol; 32%); light yellow solid; mp 98 °C (Et2O); Rf 0.53 (EtO−n-pentane, 1:3); [α]D+ 106.5 (c 1.01, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 0.11 [s, 9 H, Si(CH3)3], 0.93 (2 x d, 6 H, 3′J = 6.7 Hz, 8–H1), 1.21 (br d, 12 H, 2′H), 1.29, 1.53 (2 x d, 2 H, 3′J = 14.3, 4′J = 7.7 Hz, 6–H1), 1.60 (sept, 1 H, 1J = 7.7 Hz, 5–H1), 1.69 (d, 1 H, 1J = 12.5, 3′J = 6.7 Hz, 7–H1), 2.67 (d, 1 H, 1J = 9.7, 4′J = 7.7 Hz, 6′–H1), 3.40 (d, 2 H, 2′J = 13.4 Hz, PhCH2N), 3.67–4.10 (m, 4 H, 3′J = 13.4 Hz, PhCH2N), 4.20 (d, 1 H, 1J = 9.7, 2J = 1.0 Hz, 4–H1), 4.69 (br s, 1 H, OH), 7.17–7.33 (m, 10 H, Hphenyl), 7.35 (d, 1 H, 1J = 1.0 Hz, 1–H1).

13C NMR (75 MHz, CDCl3): δ = 0.6 [Si(CH3)3], 21.2 (C-2′), 22.9, 23.3 (C-8), 26.5 (C-7), 35.5 (C-6), 46.2 (C-1′), 53.5 ([PhCH2]3N), 60.1 (C-5), 74.5 (C-4), 110.3 (C-1′), 127.3, 128.5, 128.8, 129.3, 139.1 (Cphenyl), 153.1 (NC≡O), 200.1 (C-2′).


**Compound 12d**

Yield: 887 mg (1.61 mmol; 32%); light yellow oil; Rf 0.29 (Et2O−n-pentane, 1:3); [α]D+ 51.3 (c 1.00, CHCl3).

1H NMR (400 MHz, CDCl3): δ = 0.01 [s, 9 H, Si(CH3)3], 0.64, 0.90 (2 x d, 6 H, 3′J = 6.5 Hz, 8–H1), 1.14, 1.68 (2 x d, 2 H, 3′J = 13.8, 4′J = 3.3 Hz, 6–H1), 1.17 (br d, 12 H, 2′H), 1.96–2.12 (m, 1 H, 1J = 6.5 Hz, 7–H1), 2.28 (br s, 1 H, OH), 2.65 (d, 1 H, 1J = 1.1 Hz, 5–H1), 2J = 1.04 Hz, 5′–H1), 3.68, 4.01 (2 x d, 4 H, 2′J = 14.3 Hz, PhCH2N), 3.69–3.83 (m, 2 H, 1′–H1), 4.79–4.87 (m, 1 H, 1J = 1.1 Hz, 4–H1), 7.12–7.41 (m, 10 H, Hphenyl), 7.60 (d, 1 H, 1J = 2.5 Hz, 1–H1).

13C NMR (100 MHz, CDCl3): δ = 0.9 [Si(CH3)3], 20.5 (C-2′), 21.7, 23.9 (C-8), 24.2 (C-7), 32.9 (C-6), 46.2 (C-1′), 54.5 ([PhCH2]3N), 58.4 (C-5), 69.5 (C-4), 114.7 (C-1′), 121.2 (C-3′), 126.7, 128.0, 128.7, 140.7 (Cphenyl), 153.0 (NC≡O), 196.0 (C-2′).

(aR,AS,SS)-[5-(Dibenzylamino)-4-hydroxy-3-methyl-1,2-hexadienyl] N,N-Diisopropylcarbamate (11e) and (aR,AR,RS)-[5-(Dibenzylamino)-4-hydroxy-3-methyl-1,2-hexadienyl] N,N-Diisopropylcarbamate (12e)

According to the general procedure, the reaction of alkylnyl carbonate 1a (589 mg, 2.99 mmol) with aldehyde 9c (1.06 g, 4.18 mmol) gave 11e and 12e.

**Compound 11e**

Yield: 484 mg (1.07 mmol; 36%); colorless solid; mp 88 °C (Et2O); Rr 0.23 (Et2O–n-pentane, 1:5); [α]20D = –24.4 (c 1.01, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 1.00 (d, 3 H, J3J5 = 6.6 Hz, 6-H2), 1.21 (d, 12 H, J1J2 = 6.7 Hz, 2′-H2), 1.28 (d, 3 H, CH3), 2.79 (dq, 1 H, J1J2 = 9.8, J1J5 = 6.6 Hz, 5-H2), 3.32, 3.83, 3.85, 3.88 (2 × d, 4 H, J1J2 = 13.2 Hz, (PhCH2)2N), 3.91 (sept, 2 H, J1J2 = 6.7 Hz, 1′-H2), 3.98 (d, 1 H, J4J6 = 9.8 Hz, 4-H), 4.67 (br s, 1 H, OH), 7.16–7.36 (m, 11 H, Hphenyl, 1-H).

13C NMR (75 MHz, CDCl3): δ = 8.2 (C-6), 14.6 (CH2), 20.6 (C-2′), 46.2 (C-1′), 53.3 [(PhCH2)2N], 55.7 (C-5), 73.5 (C-4), 110.2 (C-1), 113.8 (C-3), 127.2, 128.4, 129.0, 138.6 (Cphenyl), 152.8 (NC=O), 191.9 (C-2).

Anal. Calcld for C28H38N2O3: C, 74.28; H, 8.36; N, 5.98. Found: C, 74.63; H, 8.50; N, 6.22.  

**Compound 12e**

Yield: 475 mg (1.07 mmol; 36%); colorless solid; mp 88 °C (Et2O); Rr 0.22 (Et2O–n-pentane, 1:5); [α]20D = –28.6 (c 1.03, CHCl3).

1H NMR (400 MHz, CDCl3): δ = 1.09 (d, 3 H, J3J5 = 6.8 Hz, 6-H2), 1.19 (d, 12 H, 2′-H2), 1.53 (d, 3 H, CH3), 2.22 (br s, 1 H, OH), 2.94 (dq, 1 H, J1J2 = 4.0, J1J6 = 6.8 Hz, 5-H1), 3.62 (d, 2 H, J2J3PHCH2 = 14.1 Hz, PhCH2N), 3.70–4.06 (m, 2 H, 1′-H), 3.78 (d, 2 H, J2J3PHCH2 = 14.1 Hz, PhCH2N), 4.34 (dd, 1 H, J4J6 = 4.0, J1J5 = 2.0 Hz, 4-H), 7.13–7.42 (m, 11 H, J1J4 = 2.0 Hz, Hphenyl, 1-H).

13C NMR (100 MHz, CDCl3): δ = 8.2 (C-6), 16.3 (CH3), 21.3 (C-2′), 46.5 (C-1′), 54.3 [(PhCH2)2N], 54.5 (C-4), 74.6 (C-4′), 113.6 (C-1′), 117.4 (C-3), 126.7, 128.1, 128.7, 140.4 (Cphenyl), 153.0 (NC=O), 189.1 (C-2).

Anal. Calcld for C30H44N2O3Si: 70.82; H, 8.72; N, 5.98. Found: C, 70.73; H, 8.73; N, 5.41.

(aR,AR,RS)-[5-(Dibenzylamino)-4-hydroxy-3-(trimethylsilyl)-1,2-hexadienyl] N,N-Diisopropylcarbamate (11f) and (aR,AS,SS)-[5-(Dibenzylamino)-4-hydroxy-3-(trimethylsilyl)-1,2-hexadienyl] N,N-Diisopropylcarbamate (12f)

According to the general procedure, the reaction of alkylnyl carbonate 1b (4.07 g, 15.93 mmol) with aldehyde 10a (6.41 g, 20.5 mmol) gave 11f and 12f.

**Compound 11f**

Yield: 2.50 g (4.41 mmol; 28%); colorless solid; mp 83 °C (Et2O); Rr 0.58 (Et2O–n-pentane, 1:5); [α]20D = +31.3 (c 1.03, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 0.14 [s, 9 H, Si(CH3)3], 0.97 (d, 3 H, J3J5 = 6.2 Hz, 6-H2), 1.07 [s, 9 H, Si(CH3)3], 1.19 (d, 12 H, J1J2 = 6.8 & nbsp;H2), 2.89 (d, 1 H, J1J5 = 4.5 Hz, OH), 3.60–4.20 (m, 2 H, J1J2 = 6.8 Hz, 1′-H), 3.96 (dq, 1 H, J1J5 = 6.2, J4J6 = 2.0 Hz, 4-H), 4.14 (dd, 1 H, J1J4 = 6.2, J4J5 = 4.5, J1J2 = 1.6 Hz, 4-H), 7.31–7.77 (m, 11 H, J1J4 = 1.6 Hz, Hphenyl, 1-H).

13C NMR (75 MHz, CDCl3): δ = –0.6 [Si(CH3)3], 19.3 [Si(CH3)3], 20.2 (C-6), 21.0 (C-2′), 27.1 [Si(CH3)3], 47.3 (C-1′), 72.9 (C-5), 77.2 (C-4′), 112.1 (C-1′), 117.2 (C-3), 127.5, 127.7, 129.7, 129.8, 133.4, 134.1, 135.8, 135.9 (Cphenyl), 153.1 (NC=O), 199.2 (C-2).

Anal. Calcld for C30H44N2O3Si: 67.68; H, 8.70; N, 2.47.  

Found: C, 67.39; H, 8.69; N, 2.46.

**Compound 12f**

Yield: 3.95 g (6.96 mmol; 44%); colorless solid; mp 95 °C (Et2O); Rr 0.20 (Et2O–n-pentane, 1:5); [α]20D = +75.5 (c 1.03, CHCl3).

1H NMR (300 MHz, CDCl3): δ = –0.04 [s, 9 H, Si(CH3)3], 1.06 (d, 3 H, J3J5 = 6.4 Hz, 6-H2), 1.08 [s, 9 H, Si(CH3)3], 1.19 (d, 12 H, J1J2 = 6.8 Hz, 2′-H2), 2.55 (d, 1 H, J1J5 = 2.6 Hz, OH), 3.50–4.32 (m, 2 H, J1J2 = 6.9 Hz, 1′-H), 3.97 (dq, 1 H, J1J5 = 2.8, J4J6 = 6.4 Hz, 5-H), 4.35 (dd, 1 H, J1J4 = 2.8, J4J5 = 2.6, J1J2 = 2.5 Hz, 4-H), 7.31–7.74, 7.69–7.74 (each, m, 10 H, Hphenyl), 7.55 (d, 1 H, J1J2 = 2.5 Hz, 1-H).

13C NMR (100 MHz, CDCl3): δ = –1.2 [Si(CH3)3], 15.4 (C-6), 19.2 [Si(CH3)3], 20.9 (C-2′), 27.0 [Si(CH3)3], 46.1 (C-1′), 71.9 (C-5), 74.5 (C-4′), 113.4 (C-1′), 116.8 (C-3), 127.6, 127.7, 129.7, 129.8, 133.6, 133.7, 135.8 (Cphenyl), 153.2 (NC=O), 198.0 (C-2).

Anal. Calcld for C30H44N2O3Si: 67.68; H, 8.70; N, 2.47.  

Found: C, 67.46; H, 8.51; N, 2.33.
(a,4R,5S),-[5-(tert-Butyldiphenylsiloxy)-4-hydroxy-3-methyl-1,2-bis-phenyl] N,N-Diisopropylcarbamate (15a) and (a,R,4R,5S),-[5-(tert-Butyldiphenylsiloxy)-4-hydroxy-3-methyl-1,2-bis-phenyl] N,N-Diisopropylcarbamate (15b)

According to the general procedure, the reaction of alkyne carbamate 1a (7.13 g, 36.14 mmol) with aldehyde 10a (10.53 g, 33.7 mol) gave 15a and 15b as an inseparable mixture.

Yield: 12.3 g (24.2 mmol; 67%); R = 0.27 (Et<sub>2</sub>O-n-pentane, 1:5).

1<sup>H</sup> NMR (300 MHz, CDCl<sub>3</sub>): δ = 0.99, 1.07 (2 × d, 6 H, J<sub>2,3</sub> = 6.0 Hz, 2'-H<sub>3</sub>), 1.07, 1.08 (2 × s, 18 H, Si(C<sub>2</sub>H<sub>5</sub>))<sub>3</sub>), 1.20 (d, 24 H, J<sub>2,3</sub> = 6.5 Hz, 2'H<sub>3</sub>), 1.59, 1.82 (2 × d, 6 H, CH<sub>3</sub>), 2.44, 2.71 (2 × d, 2 H, J<sub>2,3</sub> = 4.4 Hz, J<sub>4,5</sub> = 5.5 Hz, OH), 3.74–4.05 (m, 8 H, J<sub>2,3</sub> = 4.4 Hz, J<sub>4,5</sub> = 5.5 Hz, J<sub>6,7</sub> = 6.0 Hz, J<sub>2,3</sub> = 6.5 Hz, 4'-H<sub>3</sub>, 5'-H<sub>3</sub>), 7.31–7.48, 7.64–7.74 (2 × m, 22 H, J<sub>phenyl</sub> = 1-H<sub>3</sub>).

1<sup>3</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 16.4, 17.1, 17.3, 19.4 (C<sub>6</sub>-CH<sub>3</sub>), 19.2, 19.3 (Si<sub>2</sub>CH<sub>3</sub>), 20.9 (C<sub>2</sub> -C'), 26.9, 27.0 (Si<sub>2</sub>CH<sub>3</sub>), 46.3 (C -C'), 71.1, 71.4 (C-5), 76.2, 76.8 (C-4), 112.8, 113.1 (C-1), 114.3, 115.3 (C-3), 127.5, 127.6, 127.7, 129.7, 129.8, 133.6, 133.9, 133.9, 135.8, 135.9, 135.9 (C<sub>phenyl</sub>), 152.8, 152.9 (NC=O), 152.9 (C<sub>phenyl</sub>), (NCO) = 0.99, 1.07 (2 × d, 6 H, J<sub>2,3</sub> = 6.0 Hz, 2'-H<sub>3</sub>), 1.07, 1.08 (2 × s, 18 H, Si(C<sub>2</sub>H<sub>5</sub>))<sub>3</sub>), 1.20 (d, 24 H, J<sub>2,3</sub> = 6.5 Hz, 2'H<sub>3</sub>), 1.59, 1.82 (2 × d, 6 H, CH<sub>3</sub>), 2.44, 2.71 (2 × d, 2 H, J<sub>2,3</sub> = 4.4 Hz, J<sub>4,5</sub> = 5.5 Hz, OH), 3.74–4.05 (m, 8 H, J<sub>2,3</sub> = 4.4 Hz, J<sub>4,5</sub> = 5.5 Hz, J<sub>6,7</sub> = 6.0 Hz, J<sub>2,3</sub> = 6.5 Hz, 4'-H<sub>3</sub>, 5'-H<sub>3</sub>), 7.31–7.48, 7.64–7.74 (2 × m, 22 H, J<sub>phenyl</sub> = 1-H<sub>3</sub>).

ESI (EM): m/z calcd for [C<sub>52</sub>H<sub>40</sub>N<sub>2</sub>O<sub>7</sub>Si + Na]<sup>+</sup> = 732.2889; found: 732.2898.

(a,4S,4R,5R,6R)-4,4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-3-methyl-1,2-bis-phenyl] N,N-Diisopropylcarbamate (16a) and (a,R,4R,5S,)-4,4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-3-methyl-bis-phenyl] N,N-Diisopropylcarbamate (16b)

According to the general procedure, the reaction of alkyne carbamate 1a (2.01 g, 10.18 mmol) with (+)-2,3-O-isopropylidene-d-glycerine aldehyde (1.90 g, 14.59 mmol) gave 16a and 16b as an inseparable mixture.

Yield: 2.26 g (69.0 mol, 68%); R = 0.52 (Et<sub>2</sub>O-n-pentane, 3:1).

1<sup>H</sup> NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.23 (d, 2 H, J<sub>2,3</sub> = 6.8 Hz, 2'-H<sub>3</sub>), 1.36, 1.37, 1.45, 1.46 (4 × s, 12 H, J<sub>CH</sub>-CH<sub>3</sub>), 1.92, 1.93 (d, 6 H, J<sub>2,3</sub> = 2.2 Hz, CH<sub>3</sub>), 3.74–4.27 (m, 12 H, J<sub>2,3</sub> = 2.2 Hz, 4'-H<sub>3</sub>, 5'-H<sub>3</sub>, J<sub>phenyl</sub> = 1.74, 7.45 (m, 2 H, J<sub>phenyl</sub> = 1.74).

1<sup>3</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 17.2, 17.4 (CH<sub>3</sub>), 20.8, 20.8, 25.0, 25.1, 26.4, 26.6 [J<sub>CH</sub>-CH<sub>3</sub> = 46.2 (C-1)], 65.4, 65.7 (C-6), 72.5, 72.7 (C-4), 77.6, 77.7 (C-9, 105), 119 (C-3), 112.4, 113.1 (C-1), 113.6, 114.7 (C-3), 152.7, 152.8 (NC=O), 190.1, 190.4 (C-2).

ESI (EM): m/z calcd for [C<sub>52</sub>H<sub>40</sub>N<sub>2</sub>O<sub>7</sub>Si + Na]<sup>+</sup> = 732.2889; found: 735.1986.

TBDMS-Protected 4-Hydroxyallene Carbamates 17, 23, 24

General procedure for the Preparation of Silyl Ethers

4-Hydroxyallene carbamate (1 equiv) and DMAP (5 mol%) were dissolved in anhyd CH<sub>3</sub>Cl<sub>2</sub> (10 mL/mmole) under argon, 2.6-Lutidine (1.8 equiv) and tert-butyldimethylsilyl trifluoromethane-sulfonate (1.5 equiv) were added slowly at 0 °C and the reaction mixture was allowed to stir at r.t. for 30 min. The reaction was stopped by addition of sat. aq NH<sub>4</sub>Cl (5 mL/mmol) and diluted with Et<sub>2</sub>O (10 mL/mmole). The aq phase was extracted with Et<sub>2</sub>O (3×10 mL/mmol) and dried (MgSO<sub>4</sub>). The solvent was evaporated and the residue was purified by column chromatography (silica gel; Et<sub>2</sub>O-n-pentane, 1:10).

(a,4S,4S,5S)-[4-(tert-Butyldiphenylsiloxy)-5-(dibenzylamino)-3-methyl-1,2-oxadienyl] N,N-Di-isopropylcarbamate (17)

According to the general procedure, 4-hydroxyallene 11e (0.21 mg, 0.84 mmol) was converted with 2,6-lutidine (0.17 mL, 1.51 mmol) and TBDMSOTf (0.29 mL, 1.26 mmol) into the product 17.

Yield: 453 mg (0.75 mmol; 89%); colorless oil; R<sub>f</sub> 0.44 (Et<sub>2</sub>O-n-pentane, 1:10); [α]<sub>20</sub> = +65.5 (c 0.16, CH<sub>2</sub>Cl<sub>2</sub>).
(4-Hydroxy-1,2-alkadienyl carbamates in Nazarov Cyclization to Cyclopentenones)

Silyl ether 17 (453 mg, 0.75 mmol) and TMEDA (0.14 mL, 0.92 mmol, 1.2 equiv) were dissolved in anhyd toluene (6 mL) under argon. BuLi (0.50 mL, 80 mmol, 1.1 equiv) was added slowly within 10 min at −78 °C. After the solution had been allowed to stir for an additional 80 min, a solution of (E)-2-methyl-1-phenyl-1-heptene-3-one (20a) (1 equiv) in toluene (3 × 10 mL) was added. The reaction mixture was stirred for 3 h at −78 °C and then 1 h at r.t. The reaction was stopped by the addition of MeOH (0.5 mL, 0.95 mmol) and the mixture was diluted with Et2O (10 mL) and the combined organic phases were washed (MgSO4). The solvent was evaporated and the residue was purified by column chromatography (silica gel; Et2O–n-pentane, 1:20). Yields of compound (Z,R)-25 and (Z,R)-26 are based on enone 20a.

(1H NMR (300 MHz, CDCl3): δ = 0.00 [s, 9 H, Si(CH3)3], 0.05, 0.11 [2 × s, 6 H, Si(CH3)2], 0.68 [m, 6 H, 8-H3], 0.92 [s, 3 H, CH3], 1.11 (br d, 1 H, J = 6.9 Hz, 2'-H1), 1.58 (s, 3 H, CH3), 1.60–1.78 (m, 3 H, 2-H3), 1.97, 2.18 (ddd, 1 H, 1-H'), 2.75 (ddd, 1 H, 3-H'), 3.69, 3.88 [each d, 4 H, 2-CH2], 4.29 (d, 1 H, J = 6.9 Hz, 4-H1), 7.04–7.22 (m, 10 H, Hphenyl).

(13C NMR (75 MHz, CDCl3): δ = 5.4, 4.1 [Si(CH3)3], 0.0, 0.0 [Si(CH3)2], 12.9, 18.3 [Si(CH3)3], 20.7, 24.2 (C-8), 21.4 (C-2), 23.9 (C-7), 26.3 [Si(CH3)3], 38.8 (C-6), 46.1 (C-1'), 53.9 [Ph(CH3)N], 55.9 (C-5), 79.5 (C-4), 118.8 (C-1), 115.5 (C-3), 126.6, 127.9, 129.5, 141.3 (Cphenyl), 153.9 (NC=O), 199.8 (C-2).

Anal. Caled for C47H58NO2Si (696.42): C, 80.98; H, 8.93; N, 2.01. Found: C, 80.72; H, 8.59; N, 1.99.

(E,4R,2'R,3'S)-2-Butyl-5-[2-(tert-butylidimethylsilyl)oxy]-3-(tert-butylidiphenoxy)il-4-phenylbutyldiene-3-methyl-4-phenyl-2-cyclopentene-1-one ([E,R]-26)

According to the general procedure, silyl ether 24 (650 mg, 0.95 mmol) was converted with TMEDA (0.15 mL, 0.95 mmol), BuLi (0.52 mL, 0.83 mmol) and enone 20a (128 mg, 0.64 mmol) into the product (Z,R)-26.

Yield: 118 mg (0.16 mmol; 25%); yellow oil; Rf 0.75 (Et2O–n-pentane, 1:10); [α]D20 −163.9 (c 1.01, CHCl3).

(1H NMR (400 MHz, CDCl3): δ = 0.13, 0.08 [each s, 6 H, 8-H3], 0.92, 0.97 [2 × s, 18 H, 8-Si(CH3)]), 0.89 (t, 3 H, J = 7.1 Hz, Bu-4-H), 0.99 (d, 3 H, J = 6.4 Hz, 4'-H3), 1.16–1.51 (m, 2 H, Bu-3-H, Bu-2-H), 1.79 (s, 3 H, C-3), 2.15–2.37 (m, 2 H, Bu-1-H), 4.09 (dt, 1 H, J = 4.9 Hz, 4-H1), 6.89–7.93 (m, 15 H, Hphenyl).

(13C NMR (100 MHz, CDCl3): δ = 4.8, 4.0 [Si(CH3)3], 2.4 [Si(CH3)2], 13.9 (Bu-4-C), 14.7 (3-Ch), 18.2, 19.2 [Si(CH3)2], 21.0 (C-4'), 22.6 (Bu-3-C), 23.2 (Bu-1-C), 26.2, 27.1 [Si(CH3)2], 30.6 (Bu-2-C), 54.4 (C-4), 73.0 (C-3), 73.7 (C-2), 126.6, 127.3, 128.7, 129.1, 129.3, 135.8, 136.1, 141.1, 141.6 (Cphenyl), 143.6 (C-5), 147.9 (C-2), 152.7 (C-1'), 164.5 (C-3), 196.9 (C-1).

ESI (EM): m/z calcd for C36H34O3Si (M + H)+, 739.4398; found: 739.4400.
References

(1) X-ray structure analysis.

(2) For reviews, see: (a) Patai, S. The Chemistry of Ketenes, Allenes, and Related Compounds; Wiley: Chichester, 1980.


(7) Yields of compound (Z,R)-25 and (Z,R)-26 are based on enone 20a.