A Novel Route to Iridoids: Enantioselective Syntheses of Isoiridomyrmecin and α-Skytanthine

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Dedicated to Professor Dieter Seebach on the occasion of his 65th birthday.

Abstract: Enantio- and diastereoselective syntheses of the iridoids (-)-isoiridomyrmecin and (+)-α-skytanthine from a common intermediate (6-bromo-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-2-one) were achieved. Key steps in both syntheses are conjugated nucleophilic substitutions (SN2 anti-reactions) with C1 zinc cyanocuprates.

Key words: enantioselective synthesis, cuprates, natural products, zinc, alkaloids

In the course of work on asymmetric syntheses of natural products with cis-disubstituted cyclopentane rings we have recently developed a novel approach to jasmonoids.1 We now report that this route can be extended to access iridoids, such as isoiridomyrmecin (1a) and α-skytanthine (2a) (Figure 1).2 As a rule the characteristics of iridoids are a cyclopentane moiety with an alkylated C2 appendage and a vicinal cis-C1 substituent, as well as an additional trans-C1 substituent.

The strategies for the syntheses are described in Scheme 1 by retrosynthetic analyses of isoiridomyrmecin and the typical jasmonoid 12-oxophytodienoic acid (12-OPDA). Lactones A with a leaving group X can be prepared in a few steps from the enantiomerically pure allylic lactone B.3 Both enantiomers of B are available via a route using asymmetric allylic alkylation catalyzed by (phosphanyl-oxazoline)Pd complexes.3 The C2 side chain of A constitutes the basis of the first side chain of the jasmonoids as well as of the iridoids. The second side chain, in a cis position to the first, can be introduced by a SN2 anti-reaction of lactone A with an organocopper reagent. The route to iridoids is based on the observation that the substitution product also contains an allylic moiety with a leaving group and, thus, a second SN2 anti-reaction is possible. This allows the cis,trans configurational pattern of the iri-
doids to be constructed. The success of this strategy is crucially dependent on the differing reactivities of the organocopper compounds in the first and the second substitution reaction. Using a zinc and a Grignard compound as precursors for the cuprates in the first and second substitution step, respectively, solved this problem. The successful syntheses of isoiridomyrmecin (1a) and α-skytanthine (2a) are described below.

The requisite O-protected hydroxymethylcuprate was prepared from t-butyl methyl ether by treatment with t-BuOK/t-BuLi followed by addition of ZnCl₂ and CuCN (Scheme 2, Table 1). The bromide 3 as well as the phosphates 4 and 5 were used as electrophiles in the SN₂ reaction. The phosphates are readily available on a multigram scale from the corresponding allylic alcohol (A, X = OH)⁶. The substitution reaction with bromide 3 proceeded to completion at –78 to –50 °C within ca. 12 hours. With phosphates 4 and 5 a reaction temperature of –25 °C was required. All the reactions produced the lactone 6 with perfect diastereoselectivity and in high yield.

The reaction of lactone 6 with an organocopper compound prepared from methylmagnesium chloride and CuBr·S(CH₃)₂ gave carboxylic acid 7 with a high degree of diastereo- and regioselectivity.⁷ Treatment of 7 with TFA effected ether cleavage as well as lactonization. The resultant δ-lactone was hydrogenated (rhodium/aluminum oxide) and the product 8 alkylated, by reaction of its enolate with CH₃I, with diastereoselectivity of 10:1 in favor of 1a. Recrystallization furnished isomerically pure 1a in 78% yield. The optical rotation of the synthetic (−)-1a, [α]D²¹ –62.8 (c = 1.05, CCl₄), was in excellent agreement with that reported for the natural product, [α]D²¹ –62 (c = 1.00, CCl₄). By permutation of the cyclization and alkylation steps it was possible to also obtain 1b selectively from 6,⁹ as alkylation of lactone 6 proceeded with perfect stereoselection at the convex face of the enolate.¹⁰ α-Skytanthine (2a) has been prepared from nepetalic and nepetalinic acids, of known absolute configurations, by reduction and amination.¹¹ We aimed to introduce nitrogen at an early stage in the synthesis in order to provide access to a broad range of N-containing iridoid analogs. Within the framework of the syntheses described above, this was accomplished by introducing an aminomethyl group via a suitable cuprate in the first step (Scheme 3).

Table 1  Alkoxymethylation According to Scheme 2

<table>
<thead>
<tr>
<th>No.</th>
<th>Electrophile</th>
<th>Equiv ClZn(CN)CuCH₂O-t-Bu</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rac-3</td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>2.5</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2.7</td>
<td>89</td>
</tr>
</tbody>
</table>

A corresponding copper-zinc reagent was prepared from N-bromomethylphthalimide according to a method developed by Knochel.¹² At a reaction temperature of –25 °C, the reaction of this reagent with bromide 3 contaminated with ca. 10% of the cis,trans-isomer formed via S₉2 syn-reaction; in addition, up to 30% of phthalimide (relative to N-bromomethylphthalimide) was obtained.¹³ The S₉2 syn-reaction
could be suppressed by carrying the reaction out at –50 °C.

Lactone 9 is sparingly soluble in THF; nevertheless, a suspension in THF reacted with methylcopper, prepared as described above. It was advantageous at this stage to transform the resultant carboxylic acid into the methyl ester 10, because subsequent treatment of the latter with hydrazine and then catalytic hydrogenation (rhodium/ aluminum oxide) furnished δ-lactam 11 in high yield, whilst cyclization of the free amino acid with EDC and DCC proceeded in comparatively low yield (40%).

Lactam 11 was N-alkylated, then a methyl group introduced in the α position to the carbonyl group by enolate alkylation, which proceeded with diastereoselectivity of 10:1; diastereomerically pure lactam 12 was obtained in 78% yield after recrystallization. Reduction of 12 (LiAlH4, THF, reflux) furnished pure N-alkylated, then a methyl group introduced in the α position to the carbonyl group by enolate alkylation of 9. In analogy with the synthesis of iridoid 1b described above, δ-skytanthine (2b) was prepared via diastereoselective alkylation of lactone 9.

In conclusion, we have developed a highly enantio- and diastereoselective strategy for the synthesis of iridoids. Key elements of this strategy are multiple SN2 anti-reactions of allylic intermediates with organocopper compounds.

Anhyd THF was used for all procedures.

Representative Procedures for SN2 Reactions with Zinc Cyanocuprates

(+)-(3aR,4R,6aS)-4-tert-Butoxymethyl-3,3a,4,6a-tetrahydrocyclopenta[b]furan-2-one (6)

t-BuLi (1.7 M in pentane, 2.9 mL, 4.9 mmol) was added to a cooled (–60 °C), stirred solution of freshly sublimed t-BuOK (553 mg, 4.93 mmol) in tert-butyl methyl ether (6 mL) and the resultant mixture was stirred for 1 h. Then a 1.0 M solution of ZnCl2 in Et2O (4.9 mL, 4.9 mmol) was added. The resultant colorless slurry was treated during the preparation of the organozinc compound.

(+)-(3aR,4R,6aS)-2-(2-Oxo-3,3a,4,6a-tetrahydro-2H-cyclopen-ta[b]furan-4-ylmethyl)-isoadole-1,3-dione (9)

A solution of N-bromomethylphthalimide (863.0 mg, 3.59 mmol) and LiI (232 mg, 1.32 mmol) in THF (4 mL) was added over a period of 5 min to a suspension of activated zinc dust14 (800 mg, 12.2 mmol) in THF (2.5 mL), and the resultant mixture was stirred at room temperature until complete conversion of the bromide was observed. Then, THF (2 mL) was added and the supernatant was added to a cooled (–60 °C), stirred solution of LiCl2Cu(CN) in THF (4.5 mL, 3.46 mmol). To the resultant mixture a solution of 3 (267 mg, 1.32 mmol) in THF (3 mL) was added at –65 °C, the mixture allowed to warm to –30 °C over a period of 4 h and stirred for 14 h at that temperature. Standard aqueous work-up followed by flash chromatography on silica gel (30 × 2 cm) using PE-EtOAc, 3:1 to 2:1 gave 9 (346 mg, 93%) as a colorless solid which was recrystallized from CH2Cl2–Et2O to give colorless needles, mp 180.3–181.3 °C.

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References

(1) Ernst, M.; Helmchen, G. submitted.
(9) This sequence of reactions was carried out with racemic compounds.
(13) According to control experiments, phthalimide was formed during the preparation of the organozinc compound.