Synthesis of naturally occurring α-heterocyclic compounds of biological activity*

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Abstract: The total synthesis of (−)-cabenegrin A-I was achieved via (−)-6aR,11aR maackiain, which was obtained by optical resolution of racemic maackiain using S-(−)-α-methylbenzyl isocyanate. The synthesis of rac-maackiain was performed both with the Heck oxyarylation of 7-benzyloxy-2H-chromene and the BF3·OEt2 mediated ring closure of isoflavan-4-ol derivatives, the latter of which provided much higher yields. The first enantioselective synthesis of trans-6aS,11aR-pterocarpan and its conversion to cis-6aS,11aS-pterocarpan was also presented starting from racemic 2′-benzyloxyflavanone. Their stereochemistry was deduced by circular dichroism (CD) as well as by X-ray analysis of the ketal intermediate.

INTRODUCTION

Pterocarpans are naturally occurring plant products carrying a cis-fused benzofuranyl-benzopyran ring system [1]. Many of them are phytoalexins possessing high antifungal and antibacterial activity, [2,3], and several of them have been reported to inhibit HIV-1 reverse transcriptase and the cytopathic effect of HIV-1 in cell cultures [4,5]. Furthermore, it has also been demonstrated that two representatives of these natural products, cabenegrin A-I [(−)-1] and A-II [(−)-2], are active components of a Brazilian folk medicine used against snake venoms [6]. Thus, both compounds have been found to be active in male beagle dogs (1 mg/kg i.v.) against the Bothrops atrox venom [7]. These potent antidotes have been isolated by Nakaniishi and coworkers [6] from the aqueous alcoholic extract of the root of a South American plant called “Cabeça de Negra”, and their structures have been elucidated by spectroscopic methods (UV, 1H and 13C NMR, MS). The absolute configuration of cabenegrin A-I [(−)-1] was also proposed to be 6aR,11aR on the basis of its optical data.

In order to unambiguously determine the absolute configuration of (−)-1 and examine its biological activity in comparison with that of its racemate, we set our sights on its total synthesis via (−)-maackiain [(−)-4], whose 6aR,11aR absolute configuration had been deduced by chemical correlation with (−)-6aR,11aR-trifolirhizin [(−)-3] [8].

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RESULTS AND DISCUSSION

The strategy of our synthesis was based on the well-documented [9–11] synthetic availability of rac-4. Derivatization of the hydroxy group at C-3 offers a good chance to prepare diastereoisomers with a suitable chiral auxiliary, followed by separation with chromatography or crystallization. From the known syntheses of rac-4, the one reported by Breytenbach and Rall [9] was choosed to prepare rac-4 on a multigram scale from the commercially available starting materials; resorcinol and sesamol (3,4-methylenedioxyphenol). The required 3-benzylmaackiain (rac-5) could be indeed obtained in the Heck oxyarylation reaction of 11 and 12 prepared from resorcinol and sesamol in five and two steps, respectively. However, it is to be noted that—in contrast to the reports of Breytenbach [9] and Horino [12]—our thin-layer chromatography (TLC) analysis showed that the oxyarylation reaction produced not only rac-5 but additional coupled products. Moreover, the melting point of our product [rac-5, m.p. 143–144 °C] was found to be characteristically different from that of Breytenbach’s compound (m.p. 173–174 °C).

After isolation of rac-5, the side-products were separated by preparative TLC and their structures were elucidated by spectroscopic methods [13]. Since they were found to be the regioisomers of 5 (16, 17), it could be suggested that (a) the Heck-type oxyarylation of 11 did not take place with complete regioselectivity (11 → 13a → 14 → 5) as published by Breytenbach and others, [9,12] (b) the ring-closure of the corresponding organo-palladium intermediates (13a,b), leading to the products 5 and 16, probably took place via carbocation intermediates 14 and 15, respectively (Scheme 1).

Thus, carbocation 15 not only accepts readily an electron pair of the nucleophilic hydroxyl group to form the C–O bond of 16, but also rearranges via a hydride shift to the more stable 17 which, upon

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<td>2</td>
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<td>4</td>
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<td>6</td>
<td>H</td>
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<td>9</td>
<td>—CH₂CHO</td>
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<td>10</td>
<td>—CO₂Et</td>
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reaction with the phenolic hydroxyl group, affords the dioxocine derivative 18. In the following step of the synthesis, the benzyl protecting group of rac-5 was cleaved by catalytic hydrogenation over 10 % palladium charcoal while leaving the C-11a-O bond unchanged [14] to give rac-4 in 92 % yield. Since the overall yield of this nine-step synthesis was only 5 %, another route for the preparation of rac-4 was developed [15].

Based on our previous results [16], this approach exploited the thallium(III)nitrate-mediated (TTN) oxidative rearrangement of the 2′-hydroxychalcone derivative 19 to the corresponding 3,3-dimethoxy-1,2-diarylpropan-1-one (20) whose ring-closure carried out with our method [17] resulted in isoflavone 21 in 98 % yield (Scheme 2.).

This was then reduced with NaBH₄ in methanol at room temperature to result in a mixture of the cis- and trans-isoflavan-4-ols (22a,b) whose one-pot deprotection and cyclization could be achieved with BF₃·OEt₂ in the presence of dimethylsulfide to give rac-4 in good yield (85 %).

The 23–26 diastereomer pairs were prepared for the resolution of rac-4. Although all of these were stable and crystalline and various solvent and eluents were tried for the crystallization and chromatographic separation of the diastereomer pairs, only the separation of 26a,b was successful with repeated crystallization from ethanol and with rather low yield [(−)-26a: 5 %, de% = 95, (+)-26b: 2 %, de% = 99]. Removal of the chiral auxiliary of (−)-26a by reduction with LiAlH₄ gave enantiomerically almost pure (−)-4 [ee% = 99.5 by HPLC analysis] whose absolute configuration was proved 6aR,11aR on the basis of its positive ¹Lb CD bands [310 nm (+0.8), 290 nm (+0.9)] and our chiroptical rule for pterocarps [18,19].
The regioselective introduction of the hydroxyisoprene unit at C-4 of (−)-4 was performed according to the method of Ishiguro et al. [20]. In the first step, (−)-4 was alkylated with allyl bromide in the presence of potassium carbonate to give (−)-6 in 77 % yield whose thermal Claisen rearrangement in N,N-diethylaniline at 208 °C (in contrast to Ishiguro’s result) did not give (−)-7 regioselectively, but cleavage of the benzopyrane C–O bond and loss of hydrogens at C-6a and C-11a occurred, which resulted in 27 (42 %) as depicted in Scheme 3.

This unexpected transformation of the pterocarpan skeleton could be avoided when the reaction was carried out in a sealed tube in xylene at 192 °C. At this temperature, the Claisen rearrangement takes place rather slowly but without considerable side-reaction to give a mixture of 6, 7 and 8 after 24 h from which (−)-7 (68 %) can be isolated by preparative TLC in addition to (−)-6 (20 %) and (−)-8 (3 %).
In the next step of the synthesis, (−)-7 was treated with sodium metaperiodate in dioxane in the presence of catalytic amount of OsO₄ at room temperature, which resulted in (−)-9 (34 %).

The E-olefinic side-chain of (−)-1 was stereoselectively introduced by the Wittig reaction of (−)-9 with α-ethoxycarbonyltriphenylphosphonium bromide [21] in the presence of potassium ethoxide to give (−)-10 (48 %), which was reduced with lithium aluminum hydride in diethyl ether at room temperature to afford (−)-1 in 31 % yield. The UV, NMR, and CD data of this levorotatory enantiomer were identical with those reported for cabenegrin A-I [6], and therefore this confirmed the structure and proposed 6aR,11aR configuration of (−)-cabenegrin A-I [(−)-1].

Although the total synthesis of (−)-1 could be performed via rac-4, its uneffective resolution has strongly limited the production of (−)-1 for pharmacological studies. In order to avoid the low-yield resolution of the pterocarpan skeleton, a new approach has been developed for enantioselective synthesis of pterocarpans starting from racemic 2′-benzyloxyflavanone (32). This approach was based on our observation [22] that the levorotatory flavanone (−)-2S-28 could be enantioselectively transformed to the (+)-2S,3R-dihydrobenzo[b]furan derivative (+)-2S,3R-30 via (+)-2S,3S-29 as shown in Scheme 4.

Scheme 4 (i) PIDA or TTN/HC(OMe)₃, HClO₄; (ii) LiAlH₄/Et₂O, r.t.; (iii) pTsCl/pyridine; (iv) H₂/Pd(C)/MeOH; (v) NaOMe/MeOH.

Similarly, the transformation of rac-32 to the trans-2,3-dihydrobenzo[b]furan derivative rac-33 could be performed by TTN in the presence of 70 % perchloric acid in trimethyl orthoformate (TMOF) at room temperature with 48 % yield [23]. Subsequent reduction of rac-33 by LiAlH₄ gave the primary alcohol rac-34 in high yield (97 %) which was then converted smoothly to the tosylate rac-35 (79 %). Debenzylation of rac-35 by catalytic hydrogenation afforded the phenolic derivative rac-36 which was then treated with 1N sodium methoxide in methanol to promote cyclization via S₄N₂-type reaction. TLC monitoring of this reaction indicated that only one product was formed which was identified as trans-pterocarpan (rac-31b) by comparison of its NMR data with those of the cis-isomer (rac-31a) described by us recently [24]. In good agreement with quantumchemical calculations [25] which indicated that the
cis-fused B/C-ring of pterocarpan skeleton is much more prefered (ΔΔH = −10.02 kcal/mol) than trans-isomer (31b), isomerization of the trans-isomer (carried out with p-toluenesulfonic acid in benzene at 80 °C) led to cis-pterocarpan (rac-31a) with good yield (74 %). This transformation in fact resulted in a mixture of rac-31a:rac-31b (8.5:1 respectively, detected by HPLC) whose crystallization gave pure rac-31a.

In order to prepare 31a in enantiopure form, rac-32 was resolved via the readily available chiral resolving agent (2R,3R)-butanediol (Scheme 5) [26].

![Scheme 5](image)

Scheme 5 (i) 2R,3R-butanediol/ pTsOH; H₂/Pd(C), MeOH; (iii) crystallization from hexane:benzene (16:1); (iv) BnCl/K₂CO₃, acetone; (v) 10 % HCl.

The diastereomeric ketalts of rac-32 (37a,b) were prepared with acid catalysis but they could not be separated by either chromatography or crystallization. Thus, the benzyl protective groups of the diastereomers (37a,b) were removed and their crystallization in hexane/benzene 16:1 gave the diastereomer (−)-38a, whose 2R absolute configuration was determined by X-ray analysis (Fig. 1). The benzylation of (−)-38a to (+)-37a and removal of the chiral auxiliary afforded the optically active flavanone (+)-2R-32, whose enantiomeric purity was determined by HPLC on Chiralcel-OD column. Its CD data (Δε = −3.33 at 341 nm) also confirmed the 2R absolute configuration according to the rule of Snatzke [27].

![Fig. 1](image)

Fig. 1 ORTEP diagram of the ketal (−)-38a.
Starting from (+)-R-32, the first enantioselective synthesis of the trans-6aS,11aR-pterocarpan [(+)-31b] and cis-6a,11aR-pterocarpan [(+)-31a] were performed in similar manner as described above. Since rac-39 flavanone derivative has been already prepared [15] starting from commercially available phenol derivatives such as β-resorcinaldehyde (40) and sesamol (41) (Scheme 6), it can be assumed that the above-mentioned enantioselective synthesis of pterocarpans provide an access to (−)-4 and thus to (−)-cabenegrin A-I [(−)-1] as well.

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&(44) \\
&(\text{rac-39})
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Scheme 6 (i) BnCl/K₂CO₃, acetone; (ii) Ac₂O/BF₃·OEt₂, 80 °C; (iii) KOH/DMF, r.t.; (iv) NaOAc/MeOH, Δ.

CONCLUSION

The total synthesis of (−)-6aR;11aR-cabenegrin A-I [(−)-1] was accomplished via (−)-6aR;11aR-maackiain [(−)-4], which was prepared by optical resolution of its racemic form (rac-4) using S-(−)-α-methylbenzyl isocyanate as chiral auxiliary. In order to the scale up this synthesis, an improved route to rac-4 was developed, as well as a new enantioselective approach to pterocarpans, which was based on the stereocontrolled transformation of dextrorotatory 2-benzyloxyflavanone [(+)32] to (+)-2R,3S-34.

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