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

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Abstract: The total synthesis of (–)-cabenegrin A-I was achived via (–)-6a*R*,11a*R* 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-2*H*-chromene and the $BF_3 \cdot OEt_2$ mediated ring closure of isoflavan-4-ol derivatives, the latter of which provided much higher yields. The first enantioselective synthesis of *trans*-6a*S*,11a*R*-pterocarpan and its conversion to *cis*-6a*S*,11a*S*-ptarocarpan 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 Nakanishi and coworkers [6] from the aqueous alcoholic extract of the root of a South American plant called "Cabeca de Negra", and their structures have been elucidated by spectroscopic methods (UV, ^{1}H and ^{13}C NMR, MS). The absolute configuration of cabenegrin A-I [(–)-**1**] was also proposed to be 6a*R*,11a*R* 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 6a*R*,11a*R* absolute configuration had been deduced by chemical correlation with (–)-6a*R*,11a*R*-trifolirhizin [(–)-**3**] [8].

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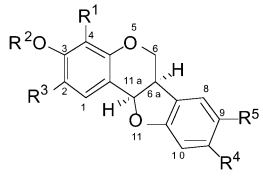

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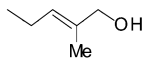
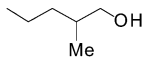
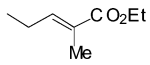
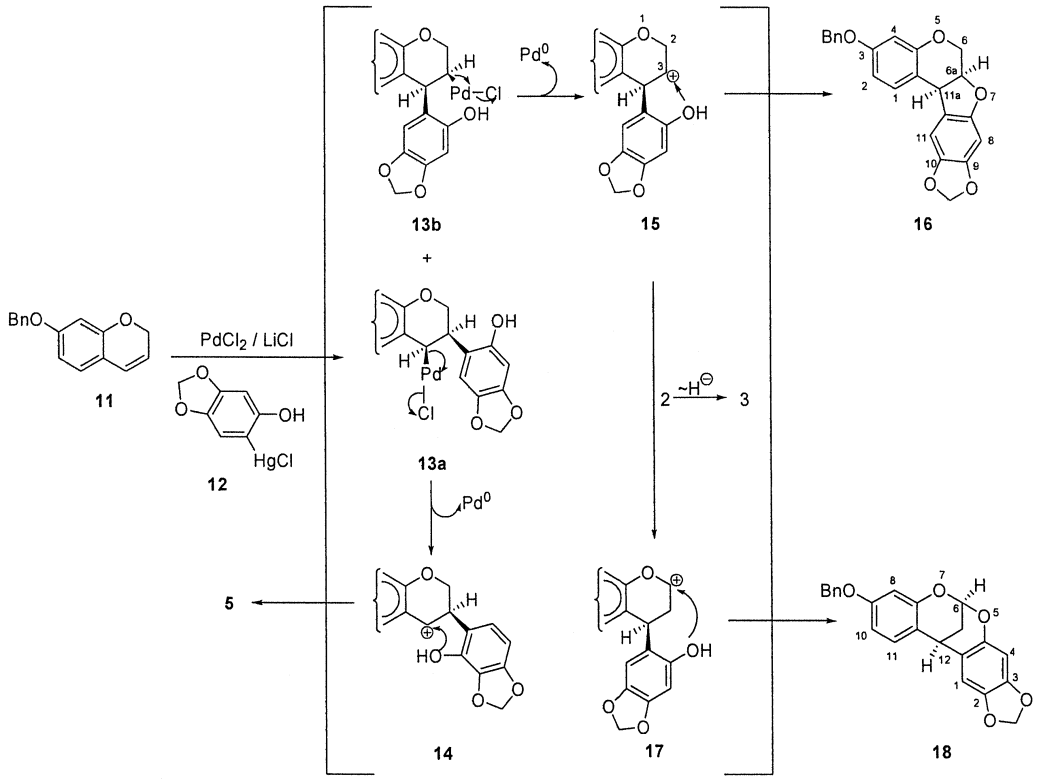
1		H	H	—O–CH_2–O—	
2	H	H		—O–CH_2–O—	
3	H	β-D-Glup	H	OMe	H
4	H	H	H	—O–CH_2–O—	
5	H	Bn	H	—O–CH_2–O—	
6	H	—CH_2–CH=CH_2	H	—O–CH_2–O—	
7	—CH_2–CH=CH_2	H	H	—O–CH_2–O—	
8	H	H	—CH_2–CH=CH_2	—O–CH_2–O—	
9	—CH_2CHO	H	H	—O–CH_2–O—	
10		H	H	—O–CH_2–O—	

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



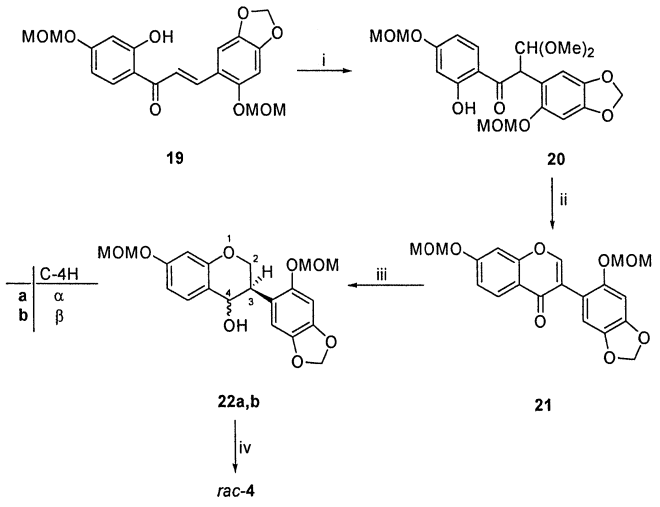
Scheme 1

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].

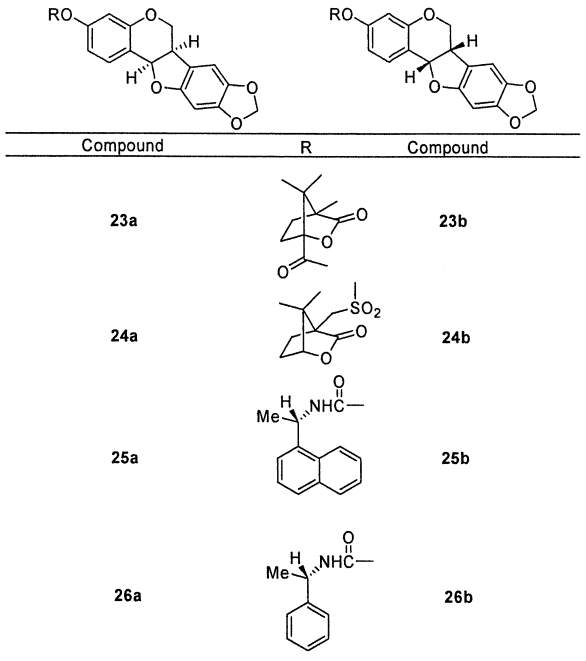
Based on our previous results [16], this approach exploited the thallium(III)nitrate-mediated (TTN) oxidative rearrangement of the 2′-hydroxychalcone derivative **19** to the corresponding 3,3-dimethoxy-1,2-diarylpropan-1-one (**20**) whose ring-closure carried out with our method [17] resulted in isoflavone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

This was then reduced with $NaBH_4$ 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 $BF_3{\cdot}OEt_2$ 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 succesful 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 $LiAlH_4$ gave enantiomerically almost pure (–)-**4** [ee% = 99.5 by HPLC analysis] whose absolute configuration was proved 6a*R*,11a*R* on the basis of its positive ^1L_b CD bands [310 nm (+0.8), 290 nm (+0.9)] and our chiroptical rule for pterocarpans [18,19].

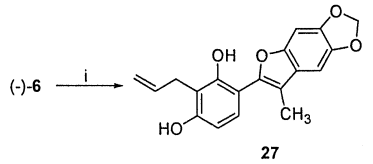


Scheme 2 (i) TTN/HC(OMe)$_3$, r.t.; (ii) NaOMe/MeOH; (iii) NaBH$_4$/MeOH; (iv) BF$_3$·OEt$_2$, Me$_2$S.



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 %).

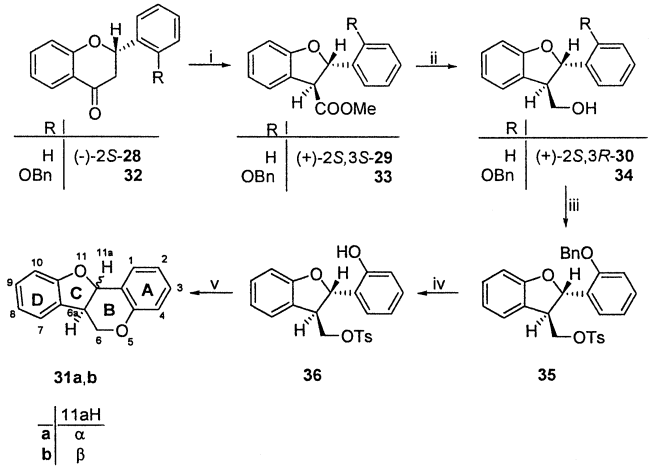


Scheme 3 (i) *N*,*N*-Diethylaniline/Δ.

In the next step of the synthesis, (–)-**7** was treated with sodium metaperiodate in dioxane in the presence of catalytic amount of OsO_4 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-ethoxycarbonylethyltriphenylphosphonium 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 6a*R*,11a*R* 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 (–)-2*S*-**28** could be enantioselectively transformed to the (+)-2*S*,3*R*-dihydrobenzo[b]furan derivative (+)-2*S*,3*R*-**30** via (+)-2*S*,3*S*-**29** as shown in Scheme 4.

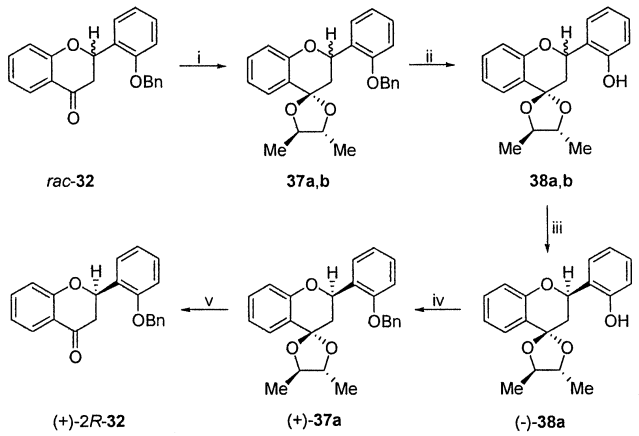


Scheme 4 (i) PIDA or TTN/$HC(OMe)_3$, $HClO_4$; (ii) $LiAlH_4/Et_2O$, r.t.; (iii) *p*TsCl/pyridine; (iv) H_2/Pd(C)/MeOH; (v) NaOMe/MeOH.

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 ortoformate (TMOF) at room temperature with 48 % yield [23]. Subsequent reduction of *rac*-**33** by $LiAlH_4$ 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 than treated with 1N sodium methoxide in methanol to promote cyclization via S_N2-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 (2*R*,3*R*)-butanediol (Scheme 5) [26].



Scheme 5 (i) 2*R*,3*R*-butanediol/*p*TsOH; H_2/Pd(C), MeOH; (iii) crystallization from hexane:benzene (16:1); (iv) BnCl/K_2CO_3,acetone; (v) 10 % HCl.

The diastereomeric ketals 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 2*R* 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 (+)-2*R*-**32**, whose enantiomeric purity was determined by HPLC on Chiralcel-OD column. Its CD data (Δε = –3.33 at 341 nm) also confirmed the 2*R* absolute configuration according to the rule of Snatzke [27].

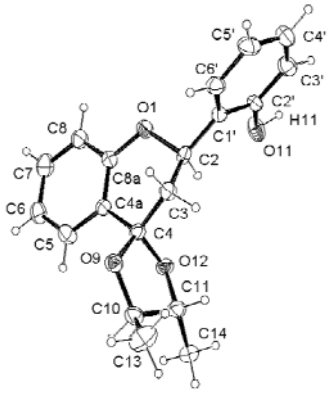
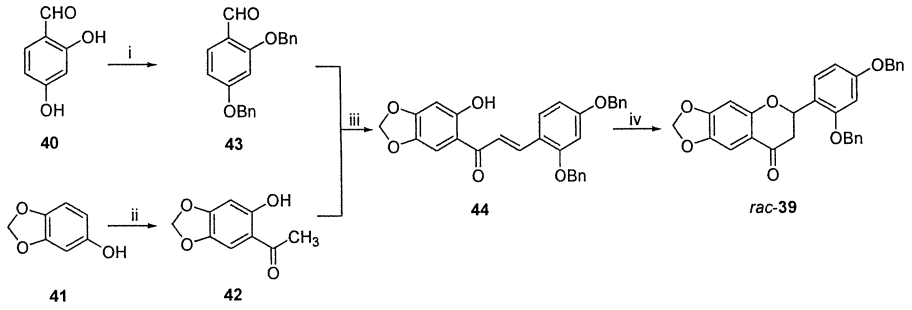


Fig. 1 ORTEP diagram of the ketal (–)-**38a**.

Starting from (+)-*R*-**32**, the first enantioselective synthesis of the *trans*-6a*S*,11a*R*-pterocarpan [(+)-**31b**] and c*is*-6a,11a*R*-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.



Scheme 6 (i) $BnCl/K_2CO_3$, acetone; (ii) $Ac_2O/BF_3{\cdot}OEt_2$, 80 °C; (iii) KOH/DMF, r.t.; (iv) NaOAc/MeOH, Δ.

CONCLUSION

The total synthesis of (–)-6a*R*;11a*R*-cabenegrin A-I [(–)-**1**] was accomplished via (–)-6a*R*;11a*R*-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 dextroratatory 2-benzyloxyflavanone [(+)-**32**] to (+)-2*R*,3*S*-**34**.

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