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Chiral syntheses of edulans I, II and dihydroedulans I, II and absolute configurations of edulans I, II

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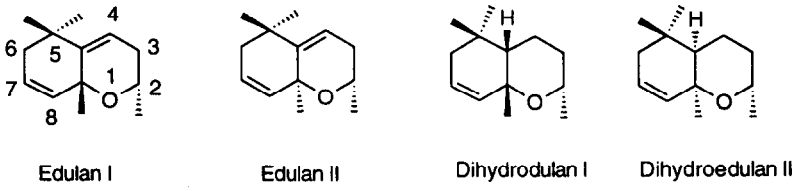
Abstract: Enantiospecific syntheses of (+)- and (−)-edulans I, II and (−)-dihydroedulans I, II, starting from (*R*)- and (*S*)-3-hydroxybutyric acid methyl esters, allowed the determination of the absolute configurations of edulans I, II. © 1997 Elsevier Science Ltd. All rights reserved.

Edulans I, II and dihydroedulans I, II, exhibiting intense rose-like aromas, are important trace components in the flavour of the purple passionfruit (*Passiflora edulis*, Sims).[1] Although their structures including relative stereochemistries were determined as shown in Figure 1 by synthesis,[2] no reports concerning the absolute configuration have appeared. As a means to determine the absolute stereochemistries and also to investigate the structure–order relationships of edulans, we initiated syntheses of edulans I, II and dihydroedulans I, II in enantiomerically pure forms.

Alkylation of the enone **1**,[3] derived from 5,5-dimethyl-1,3-cyclohexanedione by three steps,[4] with (*R*)-3-*tert*-butyldimethylsiloxybutyraldehyde **2**,[5] prepared from commercially available (*R*)-3-hydroxybutyric acid methyl ester, afforded the alcohols **3** as an inseparable mixture of diastereomers in 74% yield. The stereochemistry at the newly generated stereogenic centers of the products was not determined; however, the aldol products, without separation, were further used in the next step, since such stereogenic centers are removed at the later stage of this synthesis. Thus, the alcohols **3** were subjected to a dehydration reaction. Among the various attempts for dehydration, we found that the elimination of the trifluoroacetates **4** with DBU gave the desired enone **5** as a sole product, in good yield (58% yield, 82% yield based on the consumed starting material). The olefin geometry was assigned to be (*Z*)-form by NOE experiments between the vinylic hydrogen and the geminal methyl hydrogens. Methylation of the ketone **5** with methyllithium in tetrahydrofuran at −78°C gave the *tert*-alcohols **6** (97% yield) in a ratio of 2:1, which, on exposure to tetrabutylammonium fluoride in tetrahydrofuran furnished the diols **7** and **8** in 96% yield. After separation by silica gel column chromatography, both diols **7** and **8** were treated with boron trifluoride etherate in tetrahydrofuran at 0°C to give the ring closure products **9** and **10** (99% combined yield) in a same ratio of 2:1, respectively. The spectroscopic data of the synthetic edulans I **9** and II **10** were identical with those reported.[2b] However, the sign of the specific optical rotation of edulan I **9**, $[\alpha]_D$ −85.4 (c 0.16, CH_2Cl_2), synthesized here was opposite



Edulan I Edulan II Dihydrodulan I Dihydroedulan II

Figure 1. Structures of edulans I, II and dihydroedulans I, II.

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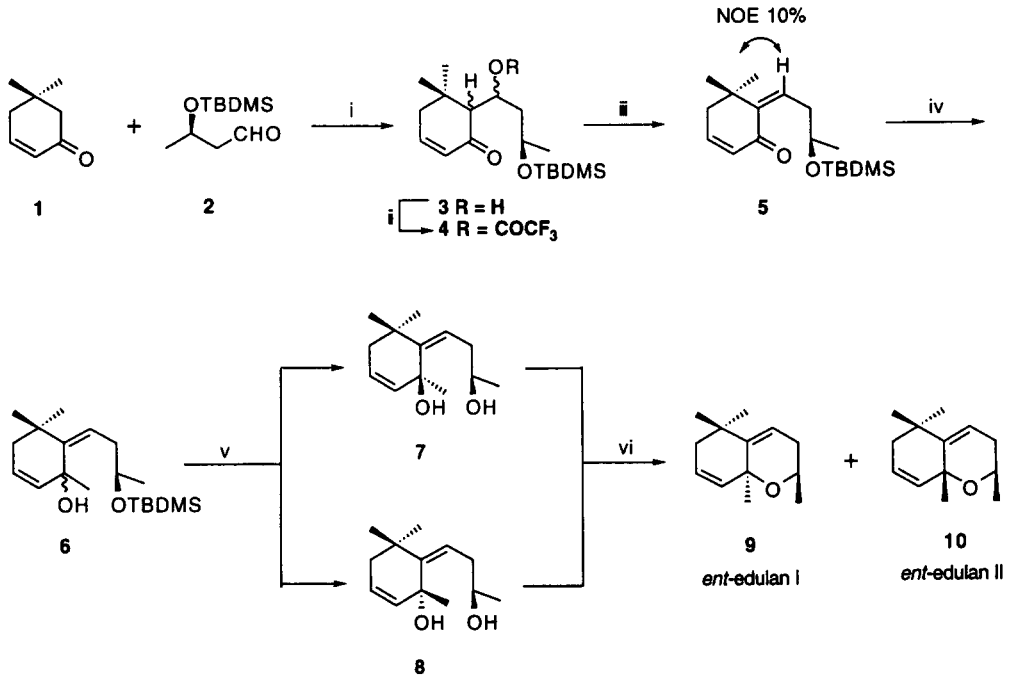
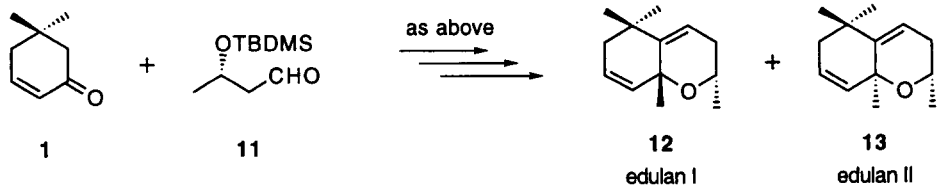
to the natural product, $[\alpha]_D$ +73.7 (c 0.08, CH_2Cl_2), isolated from fresh leaves of *Ginkgo biloba* L.[6] This result was consistent with the absolute configurations at the 2 and 8a positions of natural edulan I being (2*S*) and (8a*R*) (Scheme 1).



Scheme 1. *Reagents and conditions*: i) LDA, THF, −78°C; ii) $(CF_3CO)_2O$, Et_3N, DMAP, CH_2Cl_2, 0°C; iii) DBU, benzene, room temperature; iv) MeLi, THF, −78°C; v) Bu_4NF, THF, room temperature; vi) $BF_3 \cdot Et_2O$, THF, 0°C.

To confirm the absolute stereochemistry, a synthesis of (+)-edulan I **12** was carried out by adapting exactly the same procedure as for the synthesis of (−)-edulan I employing (*S*)-3-*tert*-butyldimethylsiloxybutyraldehyde **11** as the starting material and the specific rotation of (+)-edulan I **12**, $[\alpha]_D$ +82.8 (c 0.39, CH_2Cl_2) was identical with that of the natural product (Scheme 2).



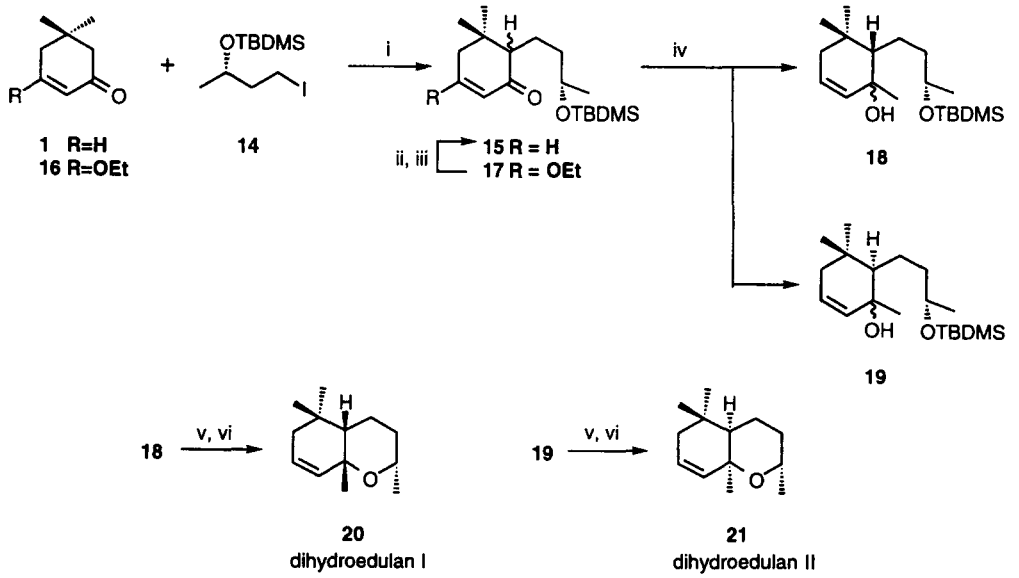
Scheme 2. Synthesis of edulans I and II.

Although the specific rotation for edulan II was not reported,[7] edulan I was isomerized into edulan II by treatment with boron trifluoride etherate[2b] suggesting that edulan II is the stereoisomer of edulan I at the 8a position.

We next carried out the synthesis of dihydroedulans I and II having the same (2*S*) configuration as that of natural (+)-edulan I. Although alkylation of the enone **1** with (*S*)-3-*tert*-butyldimethylsiloxybutyl iodide **14**[8] was investigated under various conditions, the desired product **15** was obtained in poor (13%) yield.

Therefore, the alkylation product **15** was alternatively prepared by three steps involving the alkylation of the β-ethoxy enone **16**[4] with **14**, hydrogenation of the enone **17** in the presence of 5% Rh on

alumina, and elimination of the corresponding β-ethoxy ketone, in 39% overall yield. Methylation of the ketone **15** with methyllithium afforded the diastereomeric alcohols **18** and **19** (76% yield) in a ratio of ca 1:1. Both compounds **18** and **19** were transformed into dihydroedulans I **20** and II **21** by desilylation with tetrabutylammonium fluoride followed by ring closure of the corresponding diols with boron trifluoride etherate (Scheme 3). The spectroscopic data of the synthetic dihydroedulans I **20** and II **21** were identical with those reported.[2c] Since the specific rotations for dihydroedulans I and II were not reported,[9] the absolute configurations of dihydroedulans I and II have not been determined yet.



Scheme 3. *Reagents and conditions*: i) LDA, THF, −78°C to room temperature; ii) H_2 (6.5 atm), 5% Rh on alumina, AcOEt; iii) NaH, THF, room temperature; iv) MeLi, THF, −78°C; v) Bu_4NF, THF, room temperature; vi) $BF_3 \cdot Et_2O$, THF, 0°C.

To our knowledge, this is the first asymmetric synthesis of edulans I, II and dihydroedulans I, II, and the absolute stereochemistries of edulans I and II were unambiguously determined by this synthesis.

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6. Unpublished results: The isolated natural product was identified as edulan I by comparison of the spectroscopic data with those reported.[2b]
7. The specific optical rotations of *ent*-edulan II **10** and edulan II **13** were as follows. *ent*-Edulan II: $[\alpha]_D$ −75.5 (c 0.20, CH_2Cl_2). Edulan II: $[\alpha]_D$ +73.4 (c 0.39, CH_2Cl_2).
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9. The specific optical rotations of dihydroedulan I **20** and dihydroedulan II **21** were as follows. Dihydroedulan II: $[\alpha]_D$ −38.9 (c 0.19, $CHCl_3$). Dihydroedulan II: $[\alpha]_D$ −19.6 (c 0.11, $CHCl_3$).

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