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SYNTHESIS OF (±)-PREPINNATERPENE, A BROMODITERPENE FROM THE RED ALGA LAURENCIA PINNATA YAMADA

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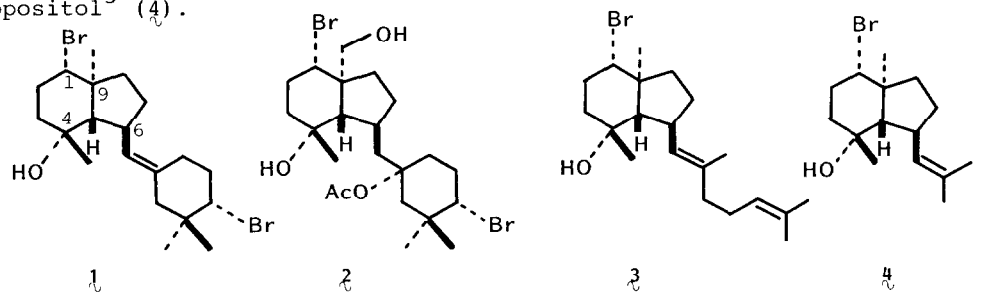
Abstract: A total synthesis of (±)-prepinnaterpene, a brominated diterpene with a unique skeleton, and (±)-oppositol, a related sesquiterpene, is described.

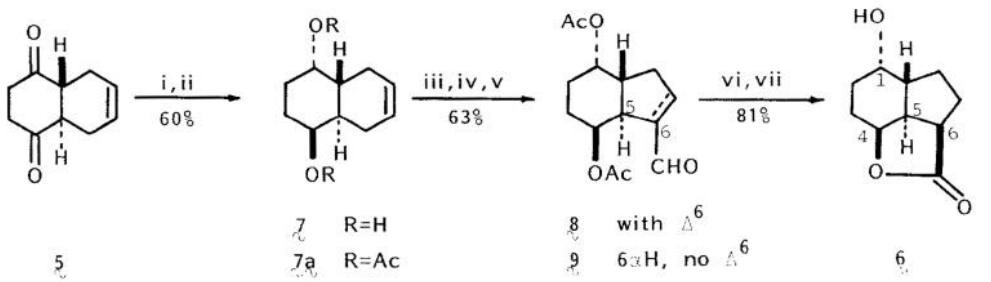
Two Laurencia species, L. irieii[1] and L. pinnata,[2] produce a group of brominated diterpenes, represented by irieol[1] (1) and pinnaterpene B[2] (2), which possess an unprecedented bicyclic skeleton with five chiral centers. The title compound, prepinnaterpene[3] (3), isolated from L. pinnata and regarded as one of the biosynthetic intermediates of these bromoditerpenes, is also characterized by the unique structure. In one of the continuing studies on synthesis of marine natural products,[4] we describe herein a stereoselective synthesis of (±)-prepinnaterpene (3) and its related sesquiterpene, (±)-oppositol[5] (4).



1 2 3 4

The synthesis involves, as an initial step, transformation of readily available trans-octalin-1,4-dione[6] (5) into 1-hydroxyperhydroindan-6,4-carbolactone[7] (6) (Scheme 1). Thus hydride reduction of the octalin (5) afforded trans-octalin-1,4-diol (7) with diaxially oriented hydroxyl groups, which was isolated as its diacetate (7a) [δ 5.62 (2H, br s)] in 60% yield. Ozonization of 7a followed by acid treatment effected cyclization, giving enal (8), which was converted into aldehyde (9) by hydrogenation with high stereoselectivity. The aldehyde (9), when submitted to Jones oxidation and subsequent deprotection, produced the lactone (6) in 81% yield.

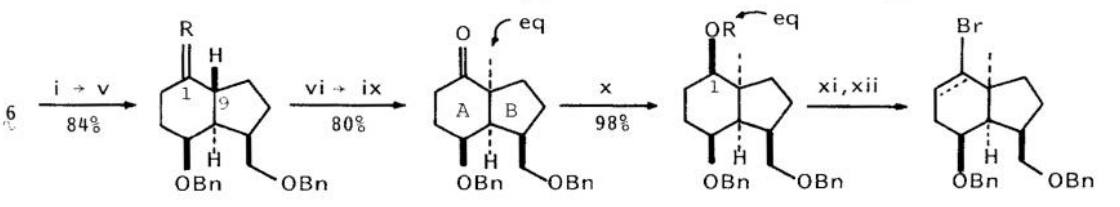
Introduction of a methyl group into the angular position (C-9) of the skeleton required formation of perhydroindan-1-one (10) with suitably protected functions (Scheme 2). The lactone (6) was transformed into triol dibenzyl ether (11) by a usual four-step process, which was then smoothly oxidized



Scheme 1. Reagents: i) $LiAlH_4$, THF, room temp, 20 min; ii) Ac_2O, Py, DMAP; iii) O_3, CH_2Cl_2, -78 °C; Zn, AcOH-H_2O; iv) p-TsOH, C_6H_6, reflux, 40 min; v) H_2, 10% Pd-C, EtOH, room temp, 0.5 h; vi) Jones reagent, acetone, 0 °C, 10 min; vii) $LiAlH_4$, THF, -20 °C, 2 h.

to yield 10. Treatment of the 1-ketone (10) according to a modification of the Ireland procedure[6b] resulted in successful methylation at C-9, giving 9-methylperhydroindan-1-one (12) with cis-fused A/B rings[8] as a single product in 80% yield. Reduction of 12 afforded 1-equatorial alcohol (13), which formed its monoacetate (13a) [δ 4.82 (1H, dd, J = 12 and 5 Hz)].

Substitution of the hydroxyl group, located on the neopentyl carbon (C-1) of the alcohol (13), with a bromine atom proceeded only with difficulty; attempted bromination under usual conditions [e.g., PBr_3 or CBr_4-$(C_6H_5)_3P$] failed, leaving tarry materials. However, treatment of 13, after mesylation, with tetrabutylammonium bromide in toluene at 95 °C for 20 h[9] produced a mixture of three compounds, from which 1-bromoperhydroindan (14) with an equatorial bromine atom [δ 4.19 (1H, dd, J = 13 and 5 Hz)] was obtained in 63% yield with its labile 1-axial epimer (15) (10%) and an olefin (16) (20%).[10]

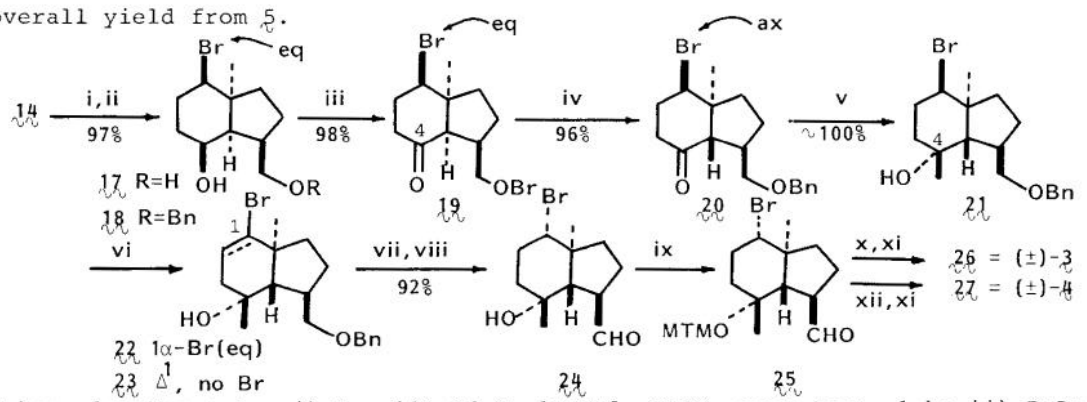


11 R=1α-OH(ax), 1β-H
10 R=O
12
13 R=H
13a R=Ac
14 1β-Br(eq)
15 1α-Br(ax)
16 Δ1, no Br

Scheme 2. Reagents: i) $EtOCH{=}CH_2$, PPTS, CH_2Cl_2, room temp, 0.5 h; ii) $LiAlH_4$, THF, 0 °C, 1 h; iii) BnBr, KH, DMF, room temp, 20 min; iv) 0.5 M HCl, room temp, 1.5 h; v) PCC, CH_2Cl_2, room temp, 1.5 h; vi) HCOOEt, NaOEt, C_6H_6, 0 °C → room temp, 40 min; vii) BuSH, p-TsOH, $MgSO_4$, C_6H_6, room temp, 16 h; viii) MeI, t-BuOK, DME, -78 °C, 1 h; ix) KOH, DEG, reflux (bath temp 130-140 °C), 10 h; x) $NaBH_4$, MeOH, 0 °C → room temp, 40 min; xi) MsCl, Et_3N, CH_2Cl_2, 0 °C, 40 min; xii) Bu_4NBr, toluene, 95-97 °C, 20 h.

The 1-bromoperhydroindan (14) was converted, via diol (17) and its monobenzyl ether (18), into bromo-4-ketone (19) with an equatorial bromine atom [δ 4.25 (1H, dd, J = 11 and 5.5 Hz)] (Scheme 3). Treatment of the cis-fused 4-ketone (19) with acid led to exclusive formation of a 1:18 inseparable mixture of 19 and its trans-fused isomer (20) with an axial bromine atom [δ 4.54 (1H, t, J = 2.5 Hz)], which was then treated with methyllithium, giving trans-fused 4-methyl-4-hydroxyperhydroindan (21) in 95% yield from 19 as a sole isolable product. The C-4 (relative) configuration of 21 was tentatively assigned as shown by the formula on the basis of the preferable equatorial approach of the reagent to the C-4 carbonyl carbon atom of 20. Since the trans-fused compound (21) also possessed the axially oriented bromine atom [δ 4.54 (1H, t, J = 2.5 Hz)], it was again submitted to S_N2 type substitution with tetrabutylammonium bromide in toluene at 115 °C for 2 d, when its equatorially brominated epimer (22) [δ 3.99 (1H, dd, J = 12 and 4 Hz)] was isolated in 55% yield with an olefin (23) (35%). Hydrogenolysis of 22 followed by oxidation afforded bromo aldehyde (24) in 92% yield, which was identical with an authentic sample[3] obtained from the Lemieux-Johnson oxidation of 3.

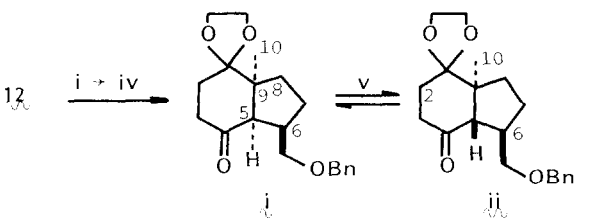
The aldehyde (24) was then converted by the Pojer procedure[11] into its methylthiomethyl ether (25), which underwent the Wittig reaction with 1,5-dimethyl-4-hexenylidenephosphorane[12,13] followed by deprotection to give a (10E)-diene (26) in 54% yield with its (10Z)-isomer (29%). Likewise, the ether (25) was treated with isopropylidenephosphorane and then deprotected to afford an olefin (27) in 95% yield. These olefins (26) and (27) were identified as (±)-prepinnaterpene (3) and (±)-oppositol (4), respectively, by comparison of the spectral data of the respective synthetic and natural samples. The present synthesis of (±)-3 involved 32 steps and amounted to 2.6% overall yield from 5.



Scheme 3. Reagents: i) H_2, 10% Pd-C, 1M HCl, EtOH, room temp, 1 h; ii) BnBr, NaH, DMF, -70 °C, 40 min; iii) PCC, CH_2Cl_2, room temp, 6 h; iv) p-TsOH (not PPTS), CH_2Cl_2, room temp, 15 h; v) MeLi, ether, -20 °C, 0.5 h; vi) Bu_4NBr, toluene, 115 °C, 2 d; vii) H_2, 10% Pd-C, 1M HCl, EtOH, room temp, 1 h; viii) PDC, CH_2Cl_2, room temp, 4 h; ix) DMSO, Ac_2O, AcOH, room temp, 10 h; x) $Ph_3P{=}C(CH_3)(CH_2)_2CH{=}C(CH_3)_2$, THF, 10 min; xi) MeI, $NaHCO_3$, acetone-H_2O, 55°C, 12 h; xii) $Ph_3P{=}C(CH_3)_2$, THF, 0 °C, 10 min.

References and Notes

1) B. M. Howard and W. Fenical, J. Org. Chem., 43, 4401 (1978).
2) A. Fukuzawa, Y. Kumagai, T. Masamune, A. Furusaki, T. Matsumoto, and C. Katayama, Chem. Lett., 1389 (1982).
3) A. Fukuzawa, Y. Takaya, H. Matsue, and T. Masamune, Chem. Lett., 1263 (1985).
4) Cf., A. Fukuzawa, H. Sato, M. Miyamoto, and T. Masamune, Tetrahedron Lett., 27, 2901 (1986).
5) S. S. Hall, D. J. Faulkner, J. Fayos, and J. Clardy, J. Am. Chem. Soc., 95, 7187 (1973).
6) a) H. B. Henbest, M. Smith, and A. Thomas, J. Chem. Soc., 3293 (1958). b) R. E. Ireland and J. A. Marshall, J. Org. Chem., 27, 1620 (1962).
7) The numbering of all synthetic perhydroindans refers to that of irieols.
8) The cis assignment to the A/B ring juncture of 12 was based on the following fact. The 1-ketone (12) was converted into 4-ketone (i), which on treatment with base afforded an 1:18 separable mixture of i and its 5-epimer (ii). Examination of the NOE difference spectra of i and ii indicated that the former (i) [hence the 1-ketone (12)] possessed cis-fused A/B rings with the angular methyl group equatorial concerning the A ring, while the latter (ii) trans-fused A/B rings.



Reagents: i) $HO(CH_2)_2OH$, p-TsOH, C_6H_6, reflux, 1 h; ii) Li, NH_3, -78 °C, 2 h; iii) BnBr, NaH, DMF, room temp, 20 min; iv) PCC, CH_2Cl_2, room temp, 1.5 h; v) NaOMe, MeOH, room temp, 21 h.

NOE: 10-H ⟷ 5α-H, 6α-H, 8α-H for i: 10-H ⟷ 2α-H, 6α-H, 8α-H for ii.

9) T. Murai, N. Shimada, T. Hirata, and T. Masamune, Meeting of Hokkaido Branch of the Chemical Society of Japan, Kitami, July 1986, Abstr., p. 33.
10) The same bromination of the mesylate of 13 at 80 °C for 16 h gave a 1:4:3 mixture of 14, 15, and 13. This result suggested that 14 would be formed by double inversion of 13 via 15, and olefin 16 would be derived from 15.
11) P. M. Pojer and S. J. Angyal, Tetrahedron Lett., 3067 (1976).
12) Transformation of (-)-germacrene-D into (±)-oppositol (4), involving a biomimetic process, has recently been reported: Y. Shizuri, S. Yamaguchi, Y. Terada, and S. Yamamura, Tetrahedron Lett., 27, 57 (1986).
13) The phosphorane was prepared as follows.

$$Cl(CH_2)_4OH \xrightarrow{i,ii} Cl(CH_2)_3CH{=}C(CH_3)_2 \xrightarrow{iii \to vi} (C_6H_5)_3P{=}C(CH_3)(CH_2)_2CH{=}C(CH_3)_2$$

Reagents: i) PCC, CH_2Cl_2, room temp, 2 h; ii) $(C_6H_5)_3P^+$-$CH(CH_3)_2$ I^-, BuLi, THF, -15°C, 0.5 h; iii) NaI, $(i\text{-}Pr)_2NEt$, acetone, reflux, 15 h; iv) $(C_6H_5)_3P$, 100°C, 7 h; v) MeI, BuLi, room temp, 15 min; vi) LDA, THF, room temp, 2 h.

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