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TOTAL SYNTHESIS OF (±)-APLYSIN-20[1)]

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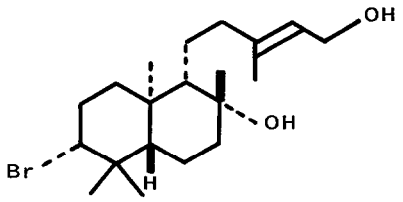
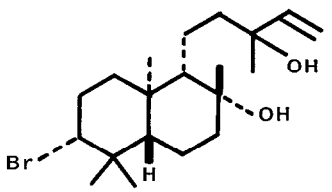
Summary: The first total synthesis of (±)-aplysin-20 involving 16 steps from nerolidol in a 10% overall yield is described.

(-)-Aplysin-20 (1)[2)] is the first brominated diterpene from marine organisms, which was isolated from Aplysia kurodai (sea hare) in 1967 by Hirata and Yamamura, and later from the red alga,[3)] a Laurencia species. The unique structure of this diterpene is characterized by the presence of an axial hydroxyl group at C-8 and an equatorial bromine atom at C-3 and by the absolute configuration which differs from that of most of terpenoids and sterols of terrestrial plant and animal origin. We report herein the first total synthesis of (+)-aplysin-20, which is based on our efficient cyclization of terminal bromohydrin of polyenes[4)] as well as on our three carbon units elongation reaction.[5)] This synthesis implies that the proposed structure should be revised for "isoconcinndiol" (2) isolated from the red alga, L. snyderae, by Howard and Fenical.[6)]



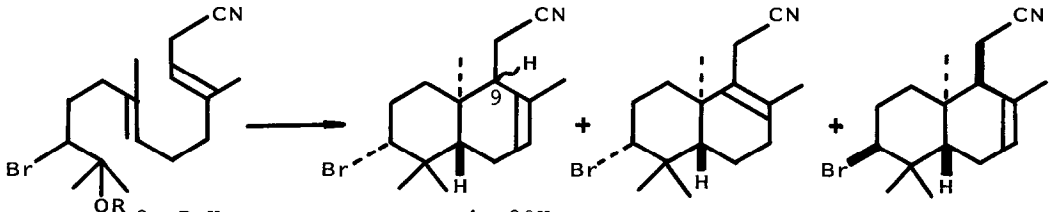
1



2

Treatment of (3E,7E)-11-bromo-12-hydroxy-4,8,12-trimethyl-3,7-tridecadienonitrile (3),[7)] prepared easily from nerolidol in three steps, with acetic trifluoroacetic anhydride[8)] in dichloromethane (CH_2Cl_2) at room temperature for 4 h afforded the corresponding acetate (3a) (~100%). Compound 3a was reacted with the boron trifluoride etherate complex under various conditions, giving a mixture of the cyclic compounds, from which four bicyclic olefins (4) ~ (7) were isolated by preparative HPLC, the results being summarized in Table 1.[9)] The nitrile (4), prepared under the conditions of run 4 or 7, was submitted to reduction (DIBAH) and subsequent Jones oxidation to afford the acid (8) (94%). Treatment of the acid with hydroiodic acid in chloroform under reflux for 4 h gave γ-lactone (9) as a single product (87%). The isomeric nitrile (5) was

Table 1.



3 R=H
3a R=Ac

4 9βH
6 9αH

5

7

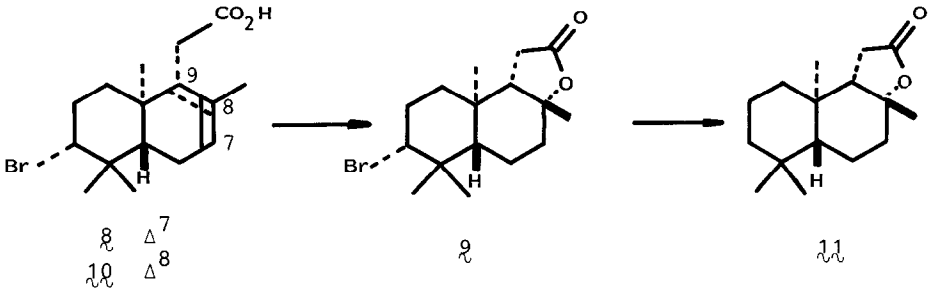
Run	acid	conditions	yield (%)[a] 4	5	6	7
1	BF_3:OEt_2	CH_2Cl_2, r.t., 30 h	19	10	9	9
2	BF_3:OEt_2	toluene, r.t., 30 h	14	6	7	10
3	BF_3:OEt_2	CH_3CN, 0 °C, 20 h	4	31	trace	trace
4	BF_3:OEt_2	PhH, reflux, 10 min	22	17	10	10
5	BF_3:OEt_2	$ClCH_2CH_2Cl$, reflux, 10 min	15	11	14	8
6	BF_3:OEt_2	CH_2Cl_2, r.t., 21 h	18	10	9	6
7	BF_3:AcOH	CH_2Cl_2, reflux, 40 min	19	17	17	14
8	BF_3:AcOH	PhH, reflux, 10 min	17	12	10	7

a) Yields were estimated by HPLC (RI).

also converted into the same γ-lactone (9), via the corresponding acid (10), according to the same procedure (75% overall yield). The lactone (9) was then reduced (Bu_3SnH-AIBN, benzene, reflux) to afford the debromolactone (11), which was identified as the known compound.[10] This establishes the structure of bromolactone (9) (Scheme 1).

Introduction of four-carbon units as the side chain was commenced with reduction of 9 ($LiAlH_4$, ether-THF, 0 °C, 30 min) to give the diol (12) (∼100%), which was converted into its monochloroacetate (12a) (∼100%) ($ClCH_2COCl$ and Py in THF, 0 °C, 15 min)[11] (Scheme 2). Compound 12a was transformed with acetic trifluoroacetic anhydride[8] under restricted conditions [CH_3CO_2H and $(CF_3CO)_2O$, CH_2Cl_2, room temp., 1 h] into the acetoxy chloroacetate (12b) (∼100% yield at

Scheme 1.

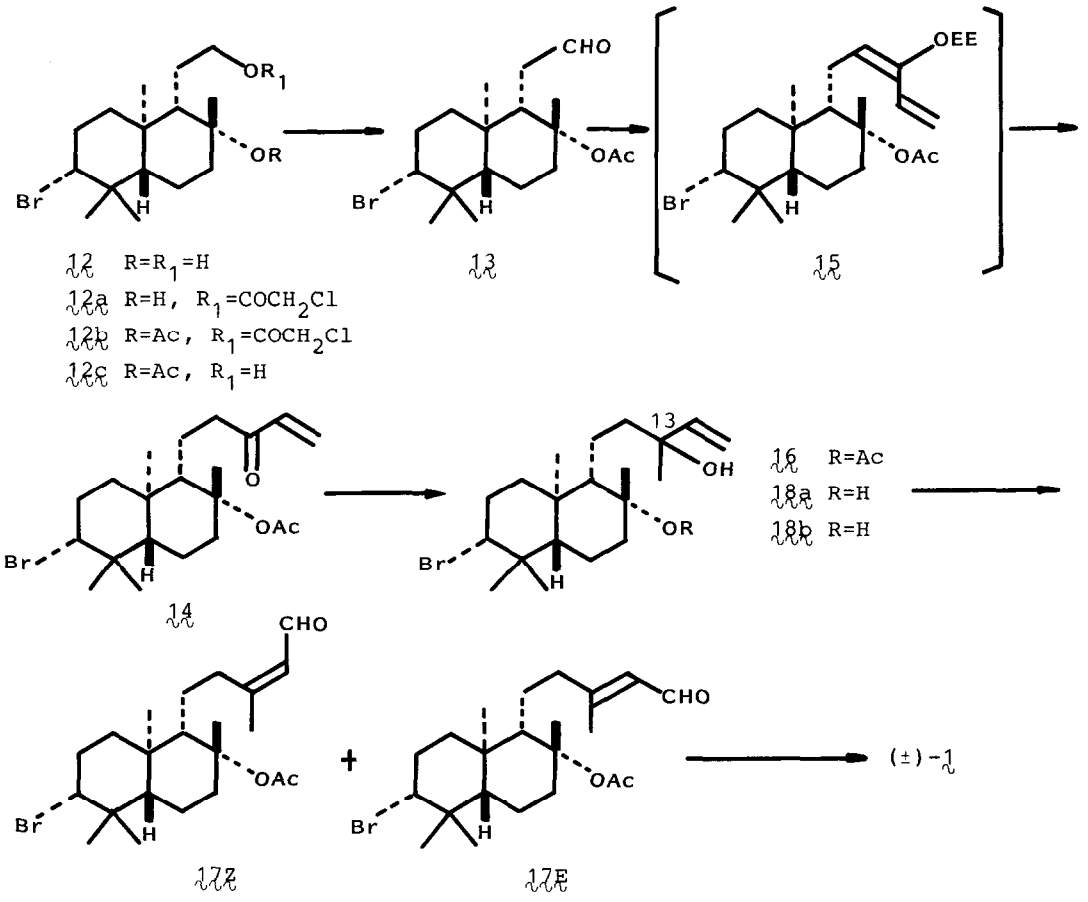


8 Δ^7
10 Δ^8

9

11

Scheme 2.



69% conversion). Compound 12b underwent selective hydrolysis ($KHCO_3$, aq MeOH) to regenerate the hydroxy acetate (12c), which on Swern oxidation[12] gave aldehyde acetate (13) (93%). A new modification of Peterson reaction[5] was employed for the elongation. Treatment of the aldehyde (13) with the titanium ate complex, prepared from 1-lithio-1-(1-ethoxyethoxy)allyltrimethylsilane and titanium(IV) isopropoxide, at -78 ∿ 20 °C for 16 h effected formation of the expected vinyl ketone (14), after hydrolysis of the resulting dienyl ether (15), in a quantitative yield. Then compound 14, when treated with methyllithium (ether, 0 °C, 15 min), produced a mixture of the diastereoisomeric allyl alcohols (16) (∿100%). Treatment of 16 with pyridinium chlorochromate (PPC)[13] in CH_2Cl_2 resulted in rearrangement with concomitant oxidation to give a 1:1 mixture of the (E)- and (Z)-α,β-unsaturated aldehydes (17E) and (17Z) (96%), which was easily separated by preparative TLC.[14] Reduction of 17E (DIBAH) afforded a new diol (1) (98%), which was identified as (±)-aplysin-20 by direct comparison (MS, IR, ^1H NMR, TLC, and HPLC) with natural (-)-aplysin-20. This synthesis involves

16 steps from nerolidol in a 10% overall yield.

The synthesis of "isoconcinndiol" (2) was also performed without difficulty. Treatment of the vinyl ketone (14) with excess of methyllithium (THF, room temp.) afforded a diol (18) (~100%) as a 1:1 mixture of diastereoisomers at C-13, which was separated by preparative HPLC (μ-Porasil) to give each diol (18a) and (18b) in pure state. However, the spectra (MS, IR, ^{1}H NMR, and TLC) of both the diols were not identical with those of the natural product by direct comparison. It follows that the proposed structure of "isoconcinndiol" should be revised.

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14) The configuration of each isomer was determined by the chemical shift of the corresponding olefinic methyl protons in the respective ^{1}H NMR spectra: (Z)-enal, δ 1.54; (E)-enal, δ 1.49.

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