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TOTAL SYNTHESIS OF UPIAL

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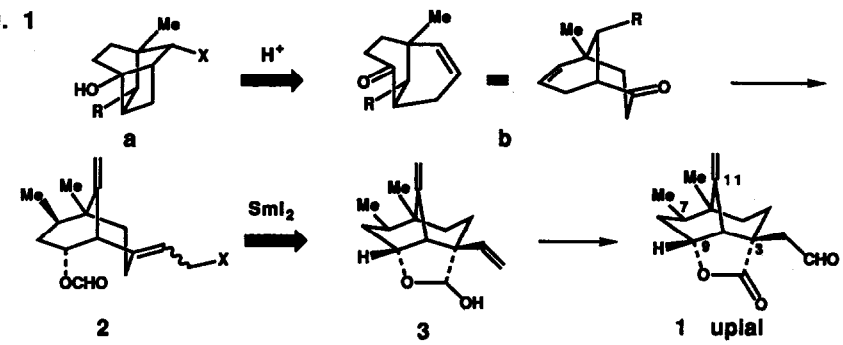
Key Words: total synthesis; marine sesquiterpene; upial; fragmentation reaction; samarium(II) iodide

Abstract: Highly stereocontrolled synthesis of marine sesquiterpene upial was achieved from D-mannitol via fragmentation reaction of tricyclic compound 10 and samarium(II) iodide-induced cyclization of diformate 2.

Upial, isolated from the sponge *Dysidea fragilis* at Kaneohe Bay, Oahu, by Scheuer *et al.* in 1979,[1] is a nonisoprenoid sesquiterpene possessing a rare bicyclo[3.3.1]nonane ring system with five asymmetric carbon centers. Its structure was first elucidated by spectral analysis and chemical transformations.[1] The absolute configuration was subsequently defined to be as shown **1** by the synthesis of (-)-upial (antipode of natural upial) from (-)-carvone by Taschner *et al.*, in 1985.[2] While investigating the synthesis of highly functionalized bicyclic natural products using fragmentation reaction of tricyclic cage compounds,[3] assessment was made of the possibility of applying to the method for the synthesizing this architecturally unique marine natural product. Herein, we wish to report a highly stereocontrolled total synthesis of upial (**1**). Our synthetic strategy involves acid-induced fragmentation reaction of tricyclic compound **a** to give bicyclo[3.3.1]nonane derivative **b** and SmI_2-induced cyclization[4] of diformate **2** to furnish the carbon skeleton of upial, as key steps (Figure 1).

Fig. 1



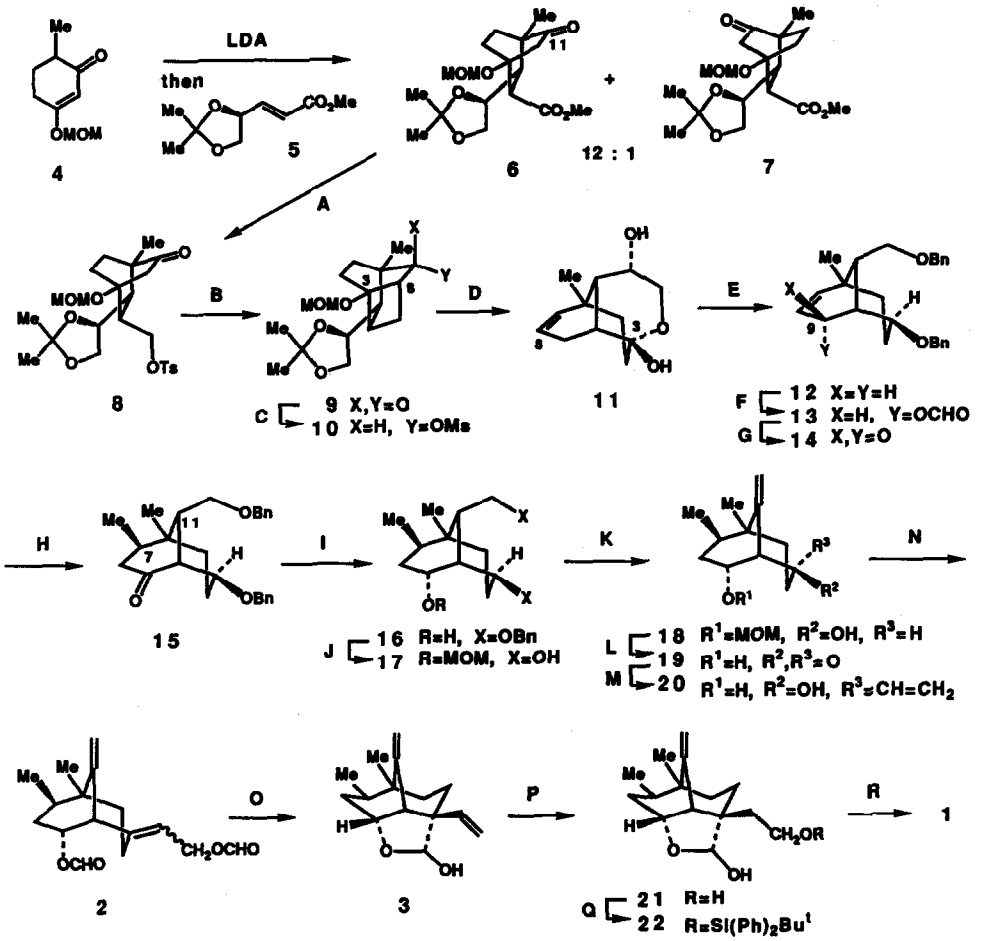
Tricyclo[3.3.1.$0^{2,7}$]nonane derivative **10**, corresponding to **a** above, was synthesized *via* sequential Michael reaction using methyl (*E,S*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-pentenoate (**5**) and base-induced intramolecular cyclization of tosylate **8**. Reaction of the kinetic enolate of 6-methyl-3-methoxymethyloxy-2-cyclohexenone (**4**)[3c] with **5** prepared from D-mannitol[5] in THF at -78°C for 1 h, -50°C for 1 h, -40°C for 1.5 h, -30°C for 12 h and -20°C for 2 h gave keto ester **6**, mp 65-6°C, $[\alpha]_D^{24}$ -85.0° (*c* 2.1, $CHCl_3$),[6,7] accompanied by the formation of a small amount of **7**, mp 68-9°C, $[\alpha]_D^{24}$ -65.4° (*c* 1.0, $CHCl_3$), in 85% yield (**6**:**7**=12:1)

(Scheme 1). The major isomer **6** was easily separated by recrystallization from ether. Ester **6** was converted to tosylate **8**, $[\alpha]_D^{24}$ +5.0° (*c* 2.0, $CHCl_3$), in three steps: 1) $LiAlH_4$ reduction to the corresponding diol as an epimeric mixture (11α-OH:11β-OH=4:1)[8]; 2) selective tosylation of the primary hydroxyl group and 3) PDC oxidation. Treatment of **8** with 1.2 equiv of potassium *tert*-butoxide in 1:1 THF-*N,N*-dimethyformamide at 0°C for 1 h gave cyclobutane **9**, mp 54-6°C, $[\alpha]_D^{24}$ -82.6° (*c* 2.1, $CHCl_3$), in 93% yield. Reduction of the ketone in **9** with $LiAlH_4$ followed by mesylation gave the first key intermediate **10**.

Cleavage of the C(3)-C(8) bond was successfully carried out by treating of **10** with a 1:1 mixture of 3*N* HCl and acetonitrile at 22°C for 24 h to afford hemiacetal **11**, mp 97-8°C, $[\alpha]_D^{24}$ +13.2° (*c* 1.0, $CHCl_3$), bearing the same carbon ring system as that of upial. The compound **11** was converted to dibenzyl ether **12**, $[\alpha]_D^{24}$ -47.0° (*c* 2.0, $CHCl_3$), in three steps: 1) $NaIO_4$ oxidation in 1:2 acetonitrile-water at 22°C to the corresponding keto aldehyde; 2) Li-liq.NH_3 reduction to the diol as a single stereoisomer and 3) protection of the hydroxyl groups as benzyl ether. Then the allylic position (C-9) in **12** was oxidized with selenium dioxide in 2:1 formic acid-1,4-dioxane at 60°C for 1.5 h to form **13**, $[\alpha]_D^{24}$ +9.0° (*c* 2.0, $CHCl_3$), in 99% yield. Successive hydrolysis of the formate in **13** with sat. NH_3 in methanol and PDC oxidation gave enone **14**, $[\alpha]_D^{24}$ -90.0° (*c* 2.0, $CHCl_3$). 1,4-Conjugated addition of **14** with dimethylcupperlithium smoothly proceeded from less hindered face with the consequent introduction of the desirable β-oriented methyl group[9] to give **15**, $[\alpha]_D^{24}$ -10.9° (*c* 1.6, $CHCl_3$), in 99% yield. The ketone in **15** was reduced with $NaBH_3CN$[10] to give α-alcohol **16**,[11] $[\alpha]_D^{24}$ -27.2° (*c* 2.0, $CHCl_3$), as a single isomer whose hydroxyl group was protected as MOM ether and whose benzyl groups were removed under reductive condition to give **17**, $[\alpha]_D^{24}$ -7.9° (*c* 2.0, $CHCl_3$). *Exo*-olefin present in upial was constructed as follows. Selective phenylsulfination of the primary hydroxyl group in **17** with $(PhS)_2$ and Bu_3P in pyridine,[12] oxidation by treatment with MCPBA to obtain the corresponding sulfoxide, and pyrolysis at 140°C in the presence of diisopropyl ethyl amine to give **18**, $[\alpha]_D^{24}$ +5.2° (*c* 2.0, $CHCl_3$), in 87% over all yield from **17**.

The second key intermediate **2** having the requisite functional groups was elaborated from **18** for constructing the skeleton of upial. Oxidation of **18** with PDC and subsequent acid hydrolysis of MOM ether produced hydroxy ketone **19**, mp 128-131°C, $[\alpha]_D^{24}$ +103.3° (*c* 1.5, $CHCl_3$). Reaction of **19** with vinylmagnesium bromide in ether was smoothly proceeded to afford allyl alcohol **20**, mp 110-2°C, $[\alpha]_D^{24}$ -36.3° (*c* 1.0, $CHCl_3$), whose secondary hydroxyl group was formylated by treatment with AcOCHO in pyridine followed by exposure to formic acid with the consequent 1,3-rearangement of the allylic hydroxyl group giving diformate **2** as a 2:1 geometrical isomer. One crucial step in the synthesis, *i. e.* the cyclization of **2** to tricyclic hemiacetal **3**, mp 61-6°C, $[\alpha]_D^{24}$ +42.1° (*c* 1.0, $CHCl_3$), was conducted in 76% yield by reaction of **2** with 3 equiv of SmI_2 in 2:1 THF-HMPA at 25°C for 30 min. The final task remaining in order to complete the synthesis of **1** was the transformation of vinyl group into acetaldehyde appendage. After several attempts at the selective hydroboration of the vinyl group, the reaction of **2** with thexylborane followed by treatment with sodium perborate[13] was found to provide **21**.[14] The primary hydroxyl group was immediately protected as silyl ether to give **22**, $[\alpha]_D^{24}$ +6.0° (*c* 1.0, $CHCl_3$). PDC oxidation of the hemiacetal in **22**, deprotection of silyl ether using Bu_4NF in THF containing 5 equiv of acetic acid and PDC oxidation completed the synthesis of upial (**1**), $[\alpha]_D^{25}$ +36.1° (*c* 0.39, $CHCl_3$). ^1H- and ^{13}C-NMR spectra and sign of optical rotation of synthesized **1** were identical to those of natural upial.[15]

Scheme 1



Reagents: A. i) $LiAlH_4$, THF, 0°C to 23°C, 94%; ii) TsCl, Py, 25°C, 85%; iii) PDC, 4Å MS, CH_2Cl_2, 25°C, 90%; B. *t*-BuOK, THF-DMF, 0°C, 1 h, 93%; C. i) $LiAlH_4$, THF, 85%; ii) MsCl, DMAP, Py, 0°C to 25°C, 97%; D. 3*N* HCl, CH_3CN, 22°C, 24 h, 91%; E. i) $NaIO_4$, CH_3CN-H_2O (1:2), 22°C, 98%; ii) Na, EtOH-liq.NH_3 (1:4), -34°C, 93% ; iii) BnBr, NaH, DMF, 25°C, 99%; F. SeO_2, HCO_2H-1,4-dioxane (2:1), 60°C, 1.5 h, 99%; G. i) 10% NH_3, MeOH, 25°C, 97%; ii) PDC, 4Å MS, CH_2Cl_2, 25°C, 85%; H. Me_2CuLi, Et_2O, -78° to -34°C, 99%; I. $NaBH_3CN$, 2*N* HCl, THF-MeOH (2:1), 0°C, 98%; J. i) $MeOCH_2Cl$, *i*-Pr_2NEt, 98%; ii) Na, liq. NH_3-THF-EtOH (20:5:1), -34°C, 95%; K. i) PhSSPh, Bu_3P, Py, 80°C, 97%; ii) MCPBA, $NaHCO_3$, CH_2Cl_2, -78°C, 95%; iii) 140°C, *i*-Pr_2NEt, 1,2-dichlorobenzene, 98%; L. i) PDC, 4Å MS, CH_2Cl_2, 24°C, 83%, ; ii) 6*N* HCl, AcOH, 23°C, 30 min, 71%; M. CH_2=CHMgBr, Et_2O, 0°C to 25°C, 87%; N. i) AcOCHO, Py, CH_2Cl_2, 0°C, 94%; ii) HCO_2H-1,4-dioxane (2:1), 22°C, 87%; O. SmI_2, THF-HMPA (2:1), 25°C, 30 min, 76%; P. thexylborane, THF, 0°C, 1 h, 25°C, 1.5 h then $NaBO_3$ $NaHCO_3$, H_2O, 25°C; Q. Ph_2(*t*-Bu)SiCl, DMAP, Et_3N, DMF, 40°C; R. i) PDC, 4Å MS, CH_2Cl_2,25°C, 75% (3 steps); ii) Bu_4NF, AcOH, THF, 25°C; iii) PDC, 4Å MS, CH_2Cl_2,25°C, 70% (2 steps).

References and Notes

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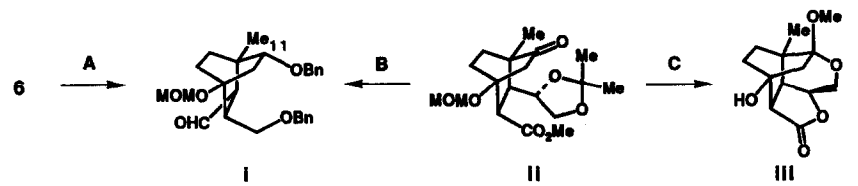
4. K. Shibuya, H. Nagaoka and Y. Yamada, *J. C. S., Chem. Commun.*, 1545 (1991).
5. α,β-Unsaturated ester **5** was prepared as follows. Oxidation of 1,2;5,6-di-*O*-isopropylidene-D-mannitol with $NaIO_4$ and 5% $NaHCO_3$ in MeOH-H_2O (2:1) at 22°C followed by treatment with $(i\text{-PrO})_2P(O)CH_2CO_2Me$ and K_2CO_3 at 0°C gave **5** and *Z*-isomer of **5** (*E*:*Z*=97:3). See also: S. Takano, A. Kurotaki, M. Takahashi and K. Ogasawara, *Synthesis*, 403 (1986).
6. Structural assignments for all stable synthetic intermediates were made based on ^{1}H-NMR (400 or 270 MHz), IR, high resolution mass spectroscopy and/or combustion analysis.
7. The stereochemistry of **6** was determined by the following chemical transformations. Keto ester **6** was transformed to **i** in four steps. The dibenzyl ether **i**, $[\alpha]_D^{24}$ -136° (*c* 1.0, $CHCl_3$), was also obtained from bicyclo[2.2.2]octane derivative **ii**, mp 105-6°C, $[\alpha]_D^{24}$ -8.5° (*c* 1.0, $CHCl_3$), prepared by sequential Michael reaction of **2** with methyl (*Z*,*S*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-pentenoate, whose stereochemistry was defined by transforming **ii** to lactone acetal **iii**, mp 133-5°C, $[\alpha]_D^{24}$ +9.4° (*c* 1.0, $CHCl_3$). Similar sequential Michael reaction has been reported by this laboratory. See: H. Nagaoka, K. Kobayashi, T. Okamura, and Y. Yamada, *Tetrahedron Lett.*, **28**, 6641 (1987).



Reagents: A. i) $LiAlH_4$, THF, 11α-OH (76%), 11β-OH (18%); ii) BnBr, NaH, DMF, 99%; iii) 80% AcOH, ; iv) $NaIO_4$, MeOH-H_2O, 71% (2 steps); B. i) L-selectride, THF, 93%; ii) $LiAlH_4$, THF, 92%, iii) BnBr, NaH, DMF, 98%; iv) 80% AcOH, 45%; iv) $NaIO_4$, MeOH-H_2O, 68%; vi) NaOH, EtOH, 87%; C. MeOH, TsOH, 70°C, 91%.

8. Numbering of compounds is in accordance with that for upial.
9. The configuration of the newly introduced methyl group was confirmed by NOE correlation between the Me proton at C-7 and the methine proton at C-11.
10. R. F. Borch and H. D. Durst, *J. Am. Chem. Soc.*, **91**, 3996 (1969).
11. Similar stereoselectivity was observed in the synthesis of (-)-upial by Taschner.[2]
12. I. Nakagawa and T. Hata, *Tetrahedron Lett.*, 1409 (1975).
13. G. W. Kabalka, T. M. Shoup and N. M. Goudgaon, *Tetrahedron Lett.*, **30**, 1483 (1989).
14. The resulting diol **21** was quite sensitive to acid and was even unstable forward silica gel. Attempts at the direct transformation of the diol to upial by various oxidation procedures were unsuccessful.
15. The absolute value of optical rotation of synthetic upial (**1**) was different from that of naturally obtained upial, $[\alpha]_D$ +92.6° (*c* 0.27, $CHCl_3$),[1] but was essentially the same as that of optically pure (-)-upial, $[\alpha]_D$ -37° (*c* 1.50, $CHCl_3$), synthesized by Taschner *et al.*[2]

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