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Total Synthesis of Dictymal, a B-seco-Dictymenoid Aldehyde from an Alga, *Dictyota dichotoma*

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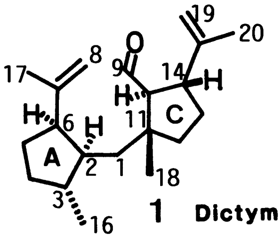
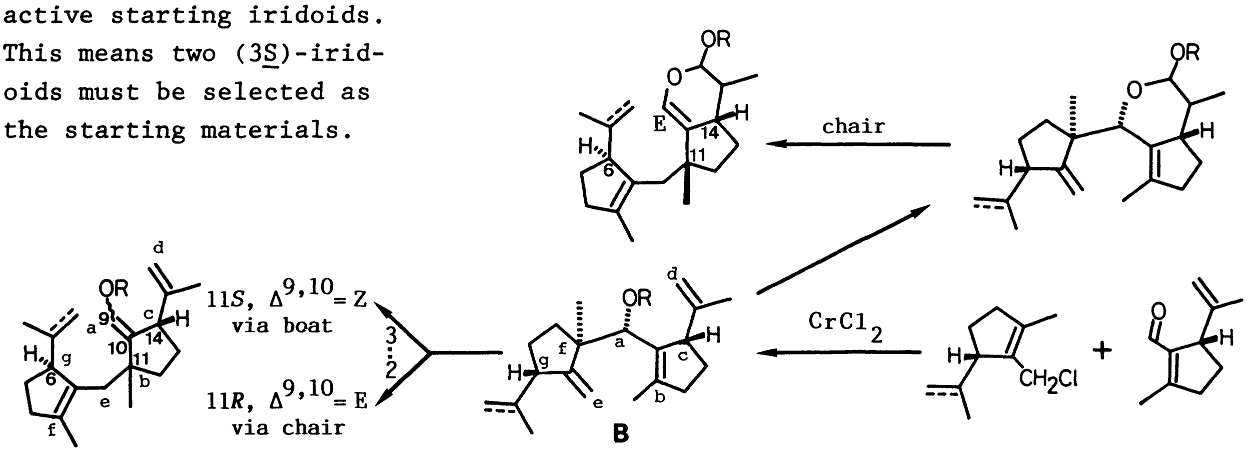
A B-seco-dictymenoid aldehyde, dictymal, was synthesized from two optically active iridoid synthons; the required ring system was constructed by lactol-regulated Cope rearrangement and stereoselective Li-tert-BuOH-in-HMPA reduction of the tetrasubstituted C=C.

Next to the recent achievement[1)] of optically active cycloaraneosene (**A**), a 5-8-5-membered tricyclic diterpene,[2)] we wish to show the total synthesis of dictymal (**1**),[3)] a unique B-seco-derivative of stereochemically different tricyclic diterpenoid from Dictyota dichotoma Lamouroux.[4)]



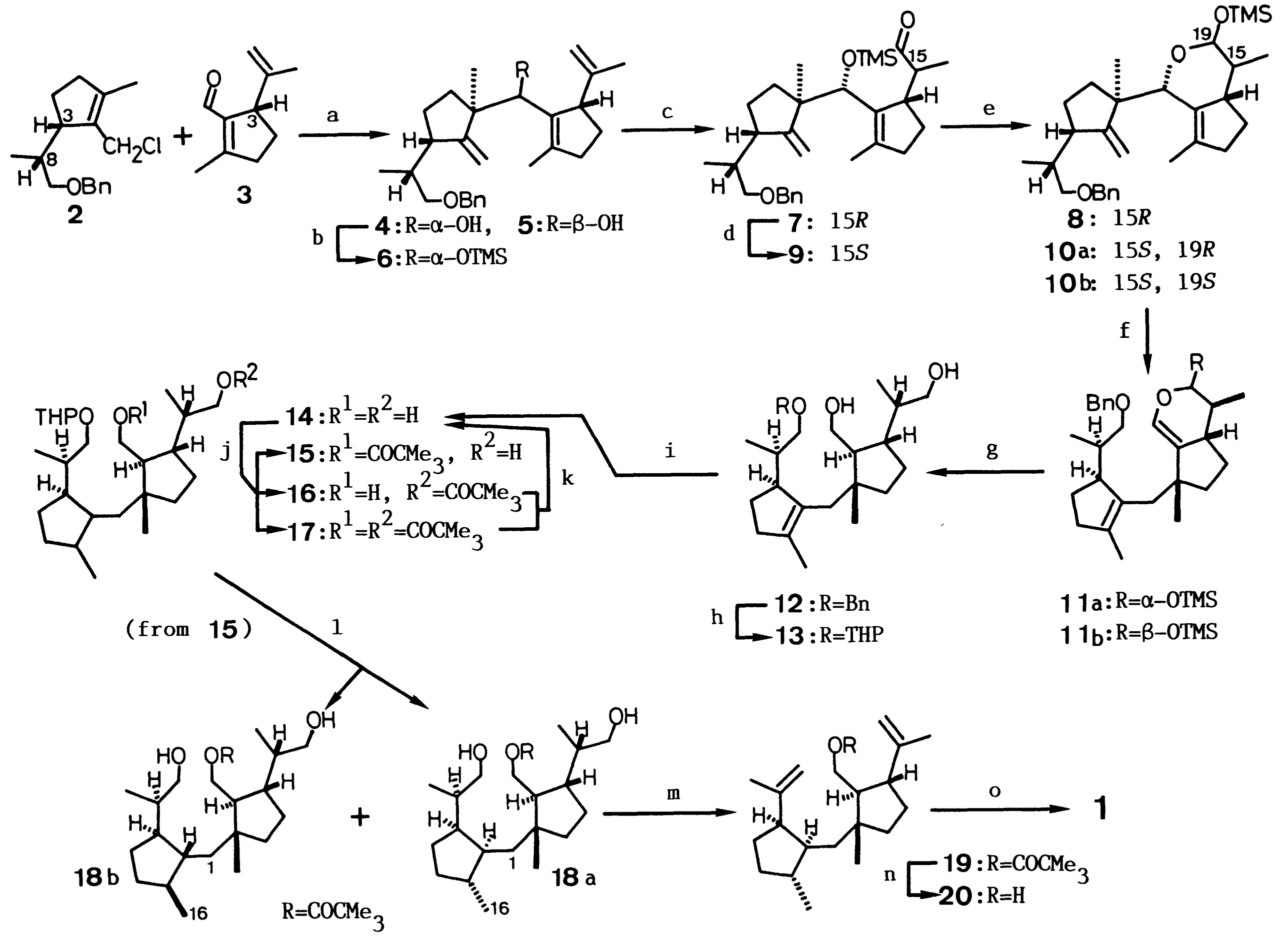
1 **Dictymal**

For the synthesis of **1**,[5)] the $CrCl_2$-mediated condensation strategy of two iridoid synthons[6)] seems to be applicable on the following retro-synthetic pathway: The relation of Me on C-11 (f in **B**) and the C_3-substituent on C-14 (g) is allways cis, and the configuration of C-6 (c) and C-14 is inherited from the optically active starting iridoids. This means two (3S)-iridoids must be selected as the starting materials.



Further, the stereochemistry of C-11 in the Cope rearrangement products can be determined by the geometry of the transition state; i.e., the retention via the boat form and the inversion via the chair form.[7)]

However, the condensates of two (3S*)- or (3R*)-iridoids are known to cause the rearrangement via both boat and chair transition states,[8)] and since the correct configuration of C-11 for **1** can only be generated via a chair transition Cope rearrangement of the condensate, it is desirable to control the transition state of the rearrangement as the chair form. "The lactol-regulated Cope rearrangement" is satisfactory for the purpose; an incorporation of the 1,5-diene to a part of cyclic systems should give only the thermolysate having E-formed enol ether. Another point in this strategy, chemical reduction of the isolated tetrasubstituted C=C in A ring, could be operated with a slightly modified procedure employed previously.[3)]



a: $CrCl_3$-LAH/THF-DMF(**4**, 62%, **5**, 17%); b: TMSCl/Py(85%); c: i) Disiamylborane, H_2O_2/OH^-(96%), ii) PCC(84%); d: KF-Florisil/MeOH(84%); e: PPTS/aqTHF, TMSCl/Py(**7**→**8**, 45%; **9**→**10a**+**10b**, 76% (2:1)); f: 180 °C/C_7H_8(**10a**→**11a**+**11b**, 81%(2:1), **10b**→**11a**+**11b**, 73%(1:4)); g: i) PPTS/aqTHF(95%), ii) $NaBH_4$/aq$NaHCO_3$-MeOH(93%); h: i) Ac_2O/Py(99%), ii) H_2/Pd-C(98%), iii) DHP, PPTS/CH_2Cl_2 (99%), iV) LAH/THF(97%); i: Li-Me_3COH/HMPA(83%); j: BuLi, Me_3CCOCl/THF(**15**; 47%, **16**; 11%; **17**, 40%); k: LAH/THF(98%); l: TsOH/MeOH(**18a**, 52%; **18b**, 37%); m: i) o-nitrophenylselenocyanate, Bu_3P/THF (97%), ii) H_2O_2/THF(86%); n: LAH/THF(95%); o:$(COCl)_2$-DMSO, Et_3N/CH_2Cl_2(95%).

The starting iridoids, (3S,8R)-9-benzyloxy-7-chloro-1-iridene (**2**) and (3S)-1,8-iridadien-7-al (**3**),[1)] were treated with $CrCl_2$ in tetrahydrofuran (THF)-dimethylformamide (DMF) to give a condensate (**4**), 62% yield, and its epimer

(**5**), 17% yield.9)

Compound **4** was converted to the corresponding trimethylsilyl (TMS) ether (**6**),10) and further to an aldehyde (**7**). The cyclic TMS acetal (**8**), obtained from **7** was subjected to the Cope rearrangement; however, **8** afforded only a trace amount of the thermolysate probably due to a steric hindrance from the axially-oriented Me on C-15 preventing the overlapping of the 1,5-diene terminals in the transition state. Therefore, **7** was converted to epimerized aldehyde (**9**), and further to a mixture of TMS acetals (**10**a and **10**b).

When **10**a and **10**b were independently heated under the Cope rearrangement conditions, a same mixture of **11**a and **11**b was formed with different ratio, indicating an epimerization at the acetal carbon. Since the same glycol (**12**) was obtained from **11**a and **11**b by consecutive treatments with PPTS and $NaBH_4$, no separation of mixtures of **10** or **11** was necessary. Compound **12** possessed the correct configuration as the ring C found in **1**. The tetrahydropyranyl (THP)-ether (**13**), prepared from **12** via a four-step sequence, was treated with Li and tert-BuOH in hexamethylphosphoric triamide (HMPA) to give a mixture of two isomeric dihydro derivatives (**14**). In order to partially protect the hydroxyl groups, **14** was treated with pivaloyl chloride to obtain a monoester (**15**) accompanied by its isomer (**16**) and diester (**17**), which were reduced to **14**. As a stereoisomeric mixture, **15** was treated with p-toluenesulfonic acid (TsOH) to afford the diols (**18**a and **18**b), which were separated by silica-gel column chromatography ($CHCl_3$-AcOEt). The major isomer **18**a was indeed the desired compound judging from the ^{13}C NMR spectroscopy.11) Dehydration of **18**a with o-nitrophenylselenocyanate12) gave a diene (**19**), which afforded an alcohol (**20**).

The Swern's oxidation of **20** yielded an aldehyde [$[\alpha]_D^{29}$ +24° (c 0.46, $CHCl_3$) (lit.6) $[\alpha]_D^{18}$ +16.4° (c 0.88, $CHCl_3$))] whose NMR [$\delta(H)^{C_6D_6}$=0.87(3H, s), 0.94 (3H, d, J=6.5 Hz), 1.56(3H, m), 1.62(3H, m), 2.35(1H, dd, J=10, 3 Hz), 2.51(1H, m), 3.00(1H, m), 4.68(1H, m), 4.76(2H, m), 4.87(1H, m), and 9.55(1H, d, J=3 Hz). $\delta(C)^{CDCl_3}$=20.5, 21.9, 22.5, 22.9, 28.5, 28.9, 31.8, 39.8, 40.4, 41.2, 45.9 (2C), 47.8, 50.2, 64.8, 110.2, 112.1, 146.7, 147.0, and 205.5] were consistent with the natural product (**1**).13)

Thus, the total synthesis of this unique metabolite is now completed.14)

References

1) N. Kato, S. Tanaka, and H. Takeshita, Chem. Lett., 1986, 1989.

2) H. J. Borschberg, Ph. D. dissertation, Eidgenossischen Technichen Hochschule, Zurich, Switzerland, 1975.

3) M. Segawa, N. Enoki, M. Ikura, K. Hikichi, R. Ishida, H. Shirahama, and T. Matsumoto, Tetrahedron Lett., 28, 3703 (1987).

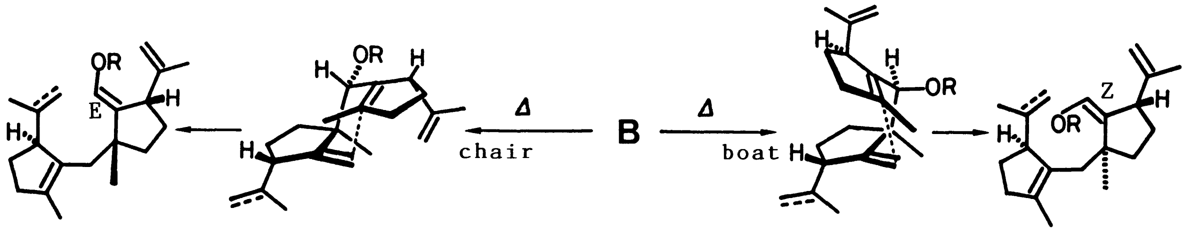
4) N. Enoki, A. Furusaki, K. Suehiro, R. Ishida, and T. Matsumoto, Tetrahedron Lett., 24, 4341 (1983).

5) To make correlations clear with previous papers, positional numbers and ring letters shown in 1 are expressed throughout in this paper.

6) H. Takeshita, T. Hatsui, N. Kato, T. Masuda, and H. Tagoshi, Chem. Lett., 1982, 1153.

7) For easy understandings, a figure showing stereochemical relationship of the

boat/chair transition geometry and the configurations of the Cope products.



8) H. Takeshita, N. Kato, K. Nakanishi, H. Tagoshi, and T. Hatsui, Chem. Lett., 1984, 1495; N. Kato, K. Nakanishi, and H. Takeshita, Bull. Chem. Soc. Jpn., 59, 1109 (1986).

9) The major product in our previous report was **5**.$^{8)}$ The condensation under careful exclusion of air and moisture, however, proceeded in favor of desired **4** giving a reversed ratio of products. Details will be discussed elsewhere.

10) All the new compounds have been fully characterized. The ^{1}H NMR data (in $CDCl_3$) of key compounds were shown as follows:

9: δ=0.03(9H, s), 0.94(3H, s), 0.98(3H, d, J=7 Hz), 1.11(3H, d, J=7 Hz), 1.86(3H, br s), 2.70(1H, m), 3.20(1H, t, J=9 Hz), 3.24(1H, br m), 3.48(1H, dd, J=9, 4 Hz), 4.20(1H, br s), 4.42(1H, d, J=12 Hz), 4.48(1H, d, J=12 Hz), 4.86(2H, d, J=2.5 Hz), 7.27(5H, br s), and 9.65(1H, s).

10a: δ=0.09(9H, s), 0.83(3H, d, J=7 Hz), 1.09(3H, d, J=7 Hz), 1.13(3H, s), 1.73 (3H, br s), 3.19(1H, t, J=9 Hz), 3.52(1H, dd, J=9, 4 Hz), 3.74(1H, br s), 4.25 (1H, d, J=8 Hz), 4.43(1H, d, J=12 Hz), 4.50(1H, d, J=12 Hz), 4.81(1H, d, J=2 Hz), 4.90(1H, d, J=2 Hz), and 7.28(5H, br s).

11a: δ=0.18(9H, s), 1.00(3H, s), 1.01(6H, d, J=7 Hz), 4.77(1H, d, J=8 Hz), 6.13 (1H, d, J=2 Hz).

12: δ=0.73(3H, s), 0.89(3H, d, J=7 Hz), 1.02(3H, d, J=7 Hz), 1.59(3H, br s), 2.70 (1H, br m), 3.09(1H, t, J=9 Hz), 3.27(1H, dd, J=9, 4 Hz), 3.29(1H, dd, J=11, 8.5 Hz), 3.42(1H, dd, J=10.5, 5 Hz), 3.61(1H, dd, J=11, 4.5 Hz), 3.71(1H, dd, J= 10.5, 5 Hz), 4.38(1H, d, J=12 Hz), 4.43(1H, d, J=12 Hz), and 7.27(5H, br s).

18a: δ=0.87(3H, d, J=7 Hz), 0.92(3H, s), 0.95(3H, d, J=7 Hz), 0.96(3H, d, J=6 Hz), 1.20(9H, s), 3.41(1H, dd, J=10.5, 7 Hz), 3.48(2H, d, J=7 Hz), 3.70(1H, dd, J=10.5, 3 Hz), 4.03(1H, dd, J=11.5, 5.5 Hz), and 4.10(1H, dd, J=11.5, 7 Hz).

19: δ=0.90(3H, s), 1.00(3H, d, J=6.5 Hz), 1.17(9H, s), 1.68(3H, br s), 1.70(3H, br s), 2.46(1H, m), 2.57(1H, m), 3.99(2H, d, J=7 Hz), 4.65(1H, m), 4.66(1H, m), 4.71(1H, br s), and 4.82(1H, br s).

20: δ=0.85(3H, s), 1.00(3H, d, J=6.5 Hz), 1.70(3H, br s), 1.75(3H, br s), 2.54 (1H, m), 2.59(1H, m), 3.59(1H, dd, J=11, 7.5 Hz), 3.66(1H, br d, J=11 Hz), 4.66 (1H, br s), 4.70(1H, m), 4.82(1H, br s), and 4.85(1H, m).

11) C-1 and C-16 of **18a** appeared at δ=39.7 and 22.8, respectively, while those of **18b** appeared at 50.8 and 21.7. See Ref. 3.

12) P. A. Grieco, Y. Masaki, and D. Boxler, J. Am. Chem. Soc., 97, 1597 (1975).

13) We are grateful to Professor Haruhisa Shirahama, Hokkaido University, who kindly performed the identification of both compounds and sent us a copy of manuscript prior to the publication.

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