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Stereoselective Synthesis of (±)-(13*E*)-2-Oxo-5α-*cis*-17α,20α-cleroda-3,13-dien-15-oic Acid, an Alleged *cis*-Clerodane Diterpenic Acid

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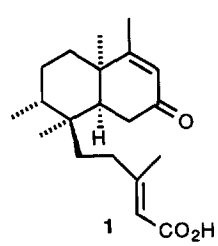
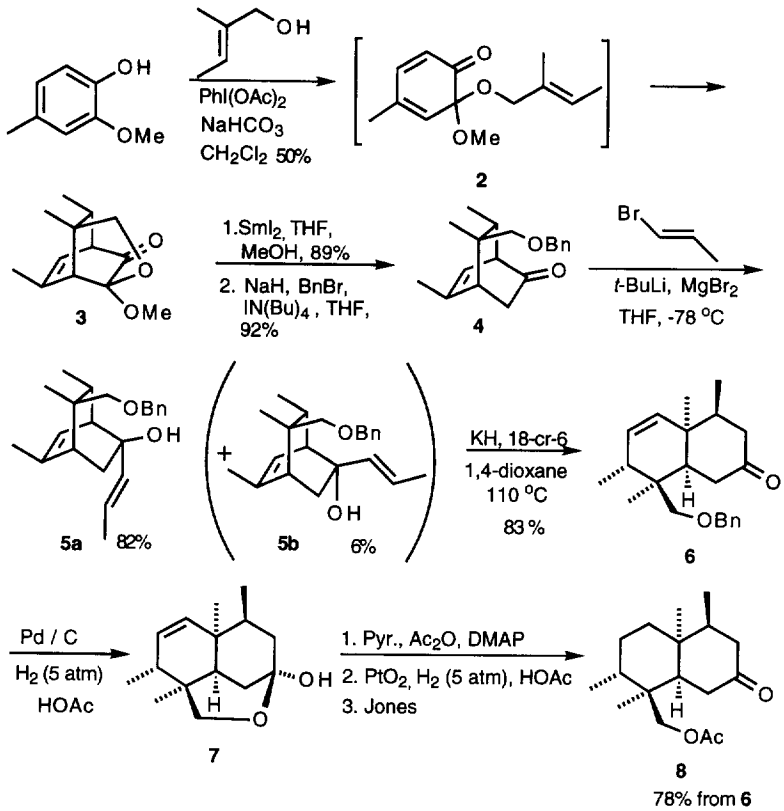
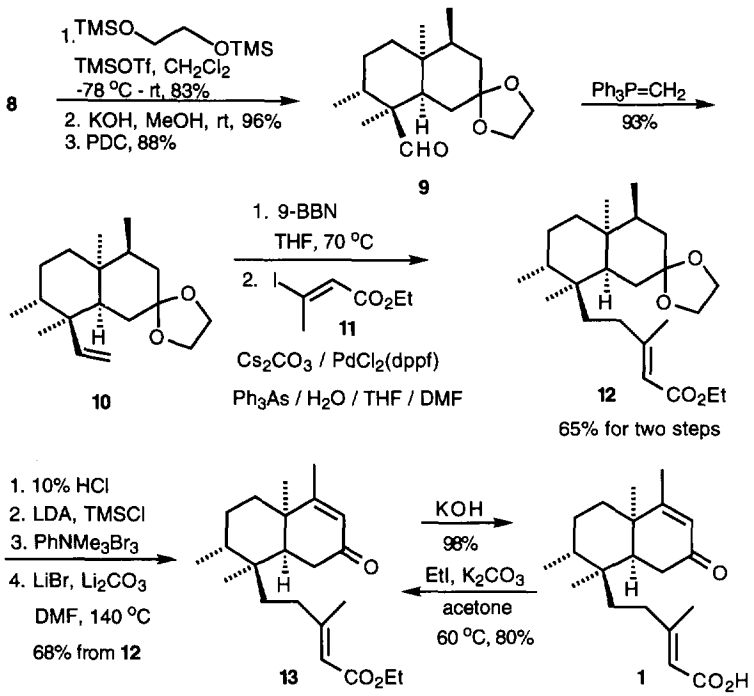
Abstract: A stereocontrolled synthesis of the title acid (±)-**1** in 19 steps and 6 % overall yield is described. The structure of (±)-**1** was confirmed by X-ray diffraction study of its ethyl ester. The structure of our synthetic (±)-**1** differs from that of the alleged natural product.

Many diterpenoids of the clerodane family posses interesting biological activities[1] and their syntheses have generated considerable interest among synthetic chemists.[2] Avila's group isolated from the seed-pods of *Eperua purpurea* Bentham[3] a diterpenic acid, which was assigned as (13*E*)-2-oxo-5α-*cis*-17α,20α-cleroda-3,13-dien-15-oic acid (**1**), possessing four stereogenic centers, four methyl groups and a side chain on the *cis*-decalin skeleton based on spectral (mainly ^{13}C NMR) correlation. We have recently reported a new methodology for the stereocontrolled synthesis of highly substituted *cis*-decalins from 2-methoxyphenol derivatives[4] using intramolecular Diels-Alder reactions of masked *o*-benzoquinones[5,6] and anionic oxy-Cope rearrangements[7] as the key steps. We wish to report the total synthesis of (±)-**1** by use of this methodology.





Tricyclic β,γ-enone **3**, with desired three methyl groups and four stereogenic centers, was obtained in 50% yield *via* a one-flask two-step process, intramolecular Diels-Alder reaction[6] of masked *o*-benzoquinone **2** produced *in situ* from oxidation of 2-methoxy-4-methylphenol with iodobenzene diacetate [$PhI(OAc)_2$] in the presence of *trans*-2-methylbut-2-en-1-ol.[8] Compound **3** was subjected to reduction with SmI_2[5,9] to give an alcohol which was benzylated with slight excess of sodium hydride and benzyl bromide to afford **4** (92%). Treatment of **4** with *trans*-1-propenyllithium, prepared from *trans*-1-bromo-1-propene *via* metal-halogen exchange with *tert*-butyllithium,[10] resulted in the formation of a 3:2 mixture of **5a** and its epimer **5b** (83% total yield); however, exposure of **4** to *trans*-1-propenyllithium in the presence of magnesium bromide afforded **5a** and **5b** in favor of **5a** (82%). Reaction of **5a** with potassium hydride in dioxane in the presence of 18-crown-6 at 110 °C for 45 min gave **6** (83%) *via* anionic oxy-Cope rearrangement. Exposure of **6** over Pd/C in HOAc and H_2 gave only hemiketal **7**. The transformation of **7** to **8** was achieved *via* acetylation of the hydroxyl group and then catalytic hydrogenation over PtO_2 in HOAc followed by Jones oxidation of the alcohol which presented partially as an over-hydrogenated product.



The conversion of **8** into **10** was achieved in 65% overall yield in the following manner: protection of the keto group under Noyori's condition[11] [bis(trimethylsilyloxy)ethane and a catalytic quantity of TMSOTf in CH_2Cl_2], deacetylation by potassium hydroxide in methanol, and then oxidation of the resulted primary alcohol with PDC in CH_2Cl_2 to yiled **9** which was subjected to the Wittig reaction to produce **10**. The palladium-catalyzed cross-coupling reaction of alkylboranes with 1-alkenyl halides, developed by Suzuki[12] and modified by Johnson and Braun,[13] would connect the side chain by exploiting the vinyl group of **10**. The introduction of side chain of **12** was accomplished in 65% yield *via* hydroboration of **10** with 9-BBN in boiling THF for 30 min and the subsequent coupling reaction between the generated 9-alkyl-9-BBN and iodide **11**[14] under Johnson and Braun's modified condition.

Ketal **12** was transformed into **13** by the following steps: acidic hydrolysis of the ketal moiety, deprotonation by LDA at -78 °C and then trapping the enolate by TMSCl, bromination of the trimethylsilyl enol ether with $PhNMe_3Br_3$ in THF and subsequent dehydrobromination.[15] Finally, treatment of **13** with potassium hydroxide afforded **1** in 98% yield. The total synthesis of **1** from 2-methoxy-4-methylphenol took 19 steps in 6% overall yield. However, the ^1H and ^{13}C NMR spectra of **1** are quite different from those of natural product.[16] We have further confirmed by means of X-ray diffraction method[17] the stereochemistry of **13** which was regenerated from **1** (K_2CO_3, EtI, acetone, 60 °C, 3 h[18]; 80% yield)

without stereochemical scrambling. Thus the exact structure of the diterpenic acid isolated by Avila's group[3] awaits further investigation.

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References and Notes:

1. Ley, S. V.; Merritt, A. T. *Natural Product Reports* **1992**, *9*, 243-287.
2. (a) Tokoroyama, T. *Yuki Gosei Kagaku Kyokai Shi* **1993**, *51*, 1164-1177; (b) Liu, H. J.; Shia, K. S.; Han, Y.; Wang, Y. *Synlett* **1995**, 545-546; (c) Piers, E.; Breau, M.; Han, Y.; Plourde, G. L.; Yeh, W. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 963-964.
3. Avila, D.; Medina, J. D. *Phytochemistry* **1991**, *30*, 3474-3475.
4. Lee, T. H.; Liao, C. C.; Liu, W. C. *Tetrahedron Lett.* **1996**, in press.
5. Liao, C. C.; Hwang, J. T. *Tetrahedron Lett.* **1991**, *32*, 6583-6586.
6. Chu, C. S.; Lee, T. H.; Liao, C. C. *Synlett* **1994**, 635-636.
7. Hill, R. K. in *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991; Vol. 5.
8. Metz, P.; Mues, C. *Tetrahedron* **1988**, *44*, 6841-6853.
9. Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705-3716.
10. Negri, J. T.; Morwick, T.; Doyon, J.; Wilson, P. D.; Huckey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 12189-12190.
11. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357-1360.
12. (a) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419-422; (b) Suzuki, A.; Miyaura, N. *Yuki Gosei Kagaku Kyokai Shi* **1993**, *51*, 1043-1052.
13. Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014-11015.
14. Chalchat, J. C.; Theron, F.; Vessiere, R. *C. R. Acad. Sci., Ser. C.* **1971**, *273*, 763-765.
15. Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1975**, *39*, 1785-1787.
16. For (±)-**1**: ^{1}H NMR ($CDCl_3$, 400MHz) δ/ppm 0.87 (s, 3H), 0.88 (d, *J*=7.2 Hz, 3H), 1.04 (dt, *J*=12.6, 4.8Hz, 1H), 1.19 (s, 3H), 1.24-1.30 (m, 1H), 1.33 (br. s, 1H), 1.45-1.48 (m, 1H), 1.57 (dt, *J*=12.6, 4.7 Hz, 1H), 1.70-1.76 (m, 2H), 1.85-1.98 (a series of m, 3H), 1.89 (s, 3H), 2.01 (s, 3H), 2.44 (dd, *J*=18.2, 3.9 Hz, 1H), 2.61 (dd, *J*=18.2, 6.3 Hz, 1H), 5.54 (s, 1H), 5.80 (s, 1H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ/ppm 14.5 (CH_3), 19.1 (CH_3), 20.7 (CH_3), 24.5 (CH_3), 26.3 (CH_2), 29.6 (CH_2), 30.4 (CH_3), 33.2 (CH), 35.4 (CH_2 x 3), 39.2 (C), 39.4 (C), 47.5 (CH), 115.5 (CH), 128.1 (CH), 162.4 (C), 169.4 (C), 171.5 (C), 199.1 (C).
17. We thank Professor Shie-Ming Peng and Mr. Gene-Hsiang Lee for the X-ray diffraction study. The result will be published in a full paper in future.
18. Welch, S. C.; Chou, C. Y.; Gruber, J. M.; Assercq, J. M. *J. Org. Chem.* **1985**, *50*, 2668-2676.

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