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A SIMPLE, HIGHLY STEREOCONTROLLED TOTAL SYNTHESIS OF (+)-HIRSUTIC ACID

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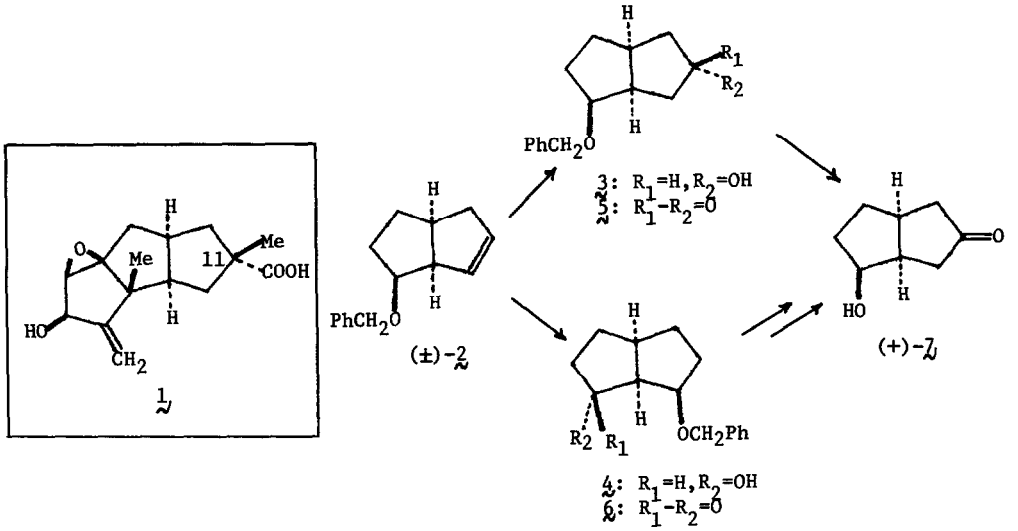
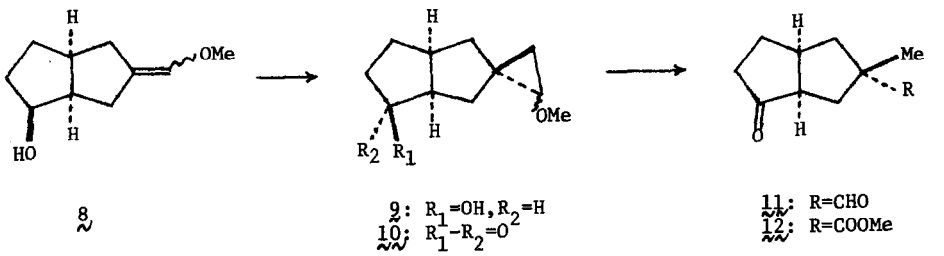
Summary: A chirally directed total synthesis of (+)-hirsutic acid from 1,3-cyclooctadiene has been accomplished in a highly stereocontrolled manner.

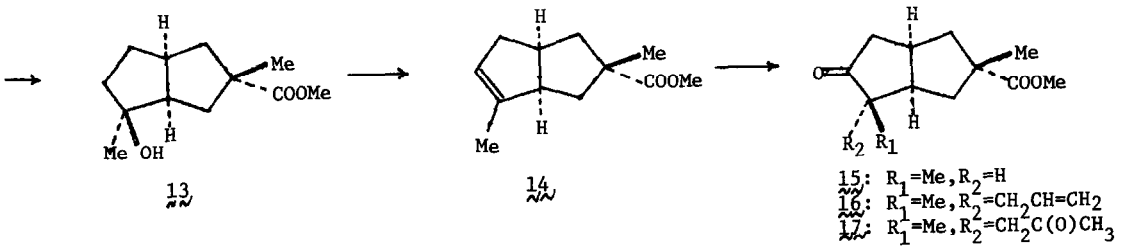
We report here a simple, highly stereocontrolled synthesis of (+)-hirsutic acid (1),[2] a representative of a novel tricyclic sesquiterpene class. Although several elegant total syntheses of *dl*-hirsutic acid (1) have appeared,[3] it seems to us that research on the simple, fully stereocontrolled synthesis of (+)-1 is still of great interest. We assumed that the highly stereocontrolled construction of the C_{11} chiral center, the key structural problem for the synthesis of 1, would be settled by utilizing a chelation-controlled carbon-carbon bond forming reaction. Accordingly, (1S,5R,6S)-6-hydroxybicyclo[3.3.0]octan-3-one (7) having the *endo*-hydroxy group was chosen as the attractive starting material for the present synthesis.

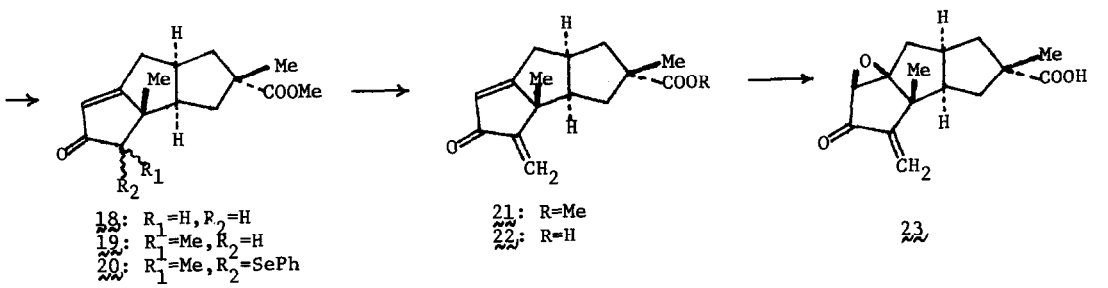
It is generally known that *cis*-bicyclo[3.3.0]octene skeletons undergo the hydroboration reaction predominantly from a convex face of molecules. Accordingly, it occurred to us that reaction of *dl*-2[4,5] with (+)-di-3-pinanylborane, followed by oxidation with alkaline hydrogen peroxide, would afford the alcohol (3) corresponding to high enantiomeric excess along with 4 having the opposite absolute configuration.[6] This was found to be the case. Treatment of *dl*-2 with 1.3 equiv of (+)-di-3-pinanylborane[7] in THF at 0-6°C for 24 hr, followed by alkaline hydrogen peroxide oxidation, resulted in the formation of the corresponding alcohols, which were roughly separated from (+)-isopinocampheol by silica gel column chromatography. Oxidation of a mixture of the alcohols with PCC in methylene chloride afforded the easily separable ketones (5 and 6). The more polar product was assigned to the desired ketone (5),[5] $[\alpha]_D^{25}$ +11°(*c* 1.18, $CHCl_3$), produced in 35% yield from *dl*-2. While the less polar ketone turned out to be 6,[5] obtained in 40% overall yield from *dl*-2. The enantiomeric excess of 6, $[\alpha]_D^{25}$-73°(*c* 0.43, $CHCl_3$), was determined by the chiral shift reagent[8] to be 60%. The desired ketone (5) was further subjected to hydrogenolysis over 5% Pd/C in methanol to afford 7,[5] $[\alpha]_D^{25}$+44°(*c* 0.30, $CHCl_3$), in quantitative yield, which was identical with an authentic material.[9] Based on the optical rotation of optically pure 7,[10] $[\alpha]_D^{25}$+55°($CHCl_3$), the hydroxy-ketone thus obtained possesses the 1S,5R,6S absolute configuration and corresponds to 80% ee. Thus, (+)-7, the key intermediate for the chiral synthesis of (+)-hirsutic acid (1), became available in large quantities and high enantiomeric purity. It should also be noted that the undesired ketone (6) is convertible to (+)-7,[11] thereby implying that the whole process described above is enantio-convergent.

The hydroxy-ketone (7), $[\alpha]_D^{25}$+44°(*c* 0.30, $CHCl_3$), 80% optical purity, was subjected to


1
(±)-2
3: R1=H, R2=OH
5: R1-R2=O
4: R1=H, R2=OH
6: R1-R2=O
(+)-7


8
9: R1=OH, R2=H
10: R1-R2=O
11: R=CHO
12: R=COOMe


13
14
15: R1=Me, R2=H
16: R1=Me, R2=CH2CH=CH2
17: R1=Me, R2=CH2C(O)CH3


18: R1=H, R2=H
19: R1=Me, R2=H
20: R1=Me, R2=SePh
21: R=Me
22: R=H
23

Wittig reaction by treatment with 2.2 equiv of (methoxymethylene)triphenylphosphorane in toluene to afford the enol ether (8)[5] in 60-70% yield based on the recovery of 7 (20-25%). Treatment of 8 with methylene iodide and zinc-copper couple in ether containing a catalytic amount of iodine (reflux temperature) afforded the cyclopropane derivative (9)[5,12] with high stereochemical control (>98%) in 73% yield. Oxidation of 9 with PCC(sodium acetate) produced the ketone (10)[5] in nearly quantitative yield, which was then treated with hydrochloric acid (35% HCl-MeOH, 1:1) at reflux temperature for 4 hr[3a] to provide the aldehyde (11). Oxidation of the aldehyde (11) with Jones reagent, followed by treatment with diazomethane, afforded 12,[5] $[\alpha]_D^{25}$-137°(*c* 0.99, $CHCl_3$), in 50% overall yield from 10. Treatment of 12 with 1.2 equiv of methyllithium in ether at -78°C gave the *tert*-alcohol (13), which was heated with potassium pyrosulfate at 120-125°C for 0.5 hr to produce the olefin (14)[5] in a fully regiocontrolled manner (76% overall yield from 12). Hydroboration of 14, followed by oxidation with PCC, gave the ketone (15)[5] regiospecifically in 61% yield. The ketone (15) was treated with 1.1 equiv of sodium hydride in DME for 1 hr, followed by the addition of allyl bromide. After stirring for 12 hr, the desired allyl-ketone (16),[5] $[\alpha]_D^{25}$+8°(*c* 1.28, $CHCl_3$), was obtained in *ca.* 70% yield. None of the isomers was observed in the reaction mixture on the careful TLC analysis. The allyl-ketone (16) was subjected to Wacker-type oxidation to afford the methyl-ketone (17),[5] $[\alpha]_D^{25}$-31°(*c* 1.31, $CHCl_3$) in 74% yield. Cyclization of 17 by treatment with base (*t*-C_4H_9OK, *t*-C_4H_9OH) resulted in the formation of the known tricycle (18),[5] $[\alpha]_D^{25}$+50°(*c* 1.87, $CHCl_3$), in 79% yield, which is a key intermediate for the synthesis of *dl*-hirsutic acid (1) reported by Matsumoto and Shirahama.[3a] Comparison of its spectral data with those of *dl*-tricycle (18) confirmed their identity.

Introduction of α-methylene functionality to the tricycle (18) succeeded in the following manner. The tricycle (18) was methylated in THF using 2 equiv of LDA and 8 equiv of methyl iodide (-78~0°) to give 19[5] in 85% yield. The methyl-ketone (19) was further treated with 2 equiv of LDA at -78° for 0.5 hr, followed by the addition of 3.2 equiv of phenylselenenyl bromide (-78~0°), to provide the selenide (20), which was oxidized with 30% hydrogen peroxide and a small amount of acetic acid in THF at 0°C, yielding the α-methylene-enone (21),[5] $[\alpha]_D^{25}$ +76.9°(*c* 0.37, $CHCl_3$), in 51% overall yield from 19. Subsequently, the carboxylic acid (22),[5] $[\alpha]_D^{25}$+67.7°(*c* 0.42, $CHCl_3$), was obtained in 88% yield by treatment of 21 with 15 equiv of anhydrous lithium iodide in refluxing DMF.[3a] Conversion of 22 to the epoxide (23),[5] $[\alpha]_D^{25}$ -66.9°(*c* 0.26, $CHCl_3$), was performed by reaction with 30% hydrogen peroxide in MeOH-H_2O containing 3 equiv of sodium hydroxide at -50~-36°C (40% yield).[3a] Finally, reduction of 23 with sodium borohydride in ethanol at 0°C[3a] provided crystalline (+)-hirsutic acid (1), mp 170°C; $[\alpha]_D^{25}$ +91°, in 74% yield. The spectral data of thus obtained (+)-1 were superimposable with those reported by Scott and his coworkers.[2] Recrystallization from ether for two times afforded optically pure (+)-hirsutic acid (1), $[\alpha]_D^{25}$+114°(*c* 0.11, $CHCl_3$), (lit.[2] $[\alpha]_D^{25}$+116°(*c* 1.05, $CHCl_3$)); mp 174~176°C, (lit.[2] mp 179~180°C).

In this way, the first asymmetric total synthesis of (+)-hirsutic acid (1) was accomplished in a highly stereocontrolled manner.

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References and Notes

1) A fellow from Mitsubishi Pharmaceutical Co. Ltd., Awaguri, Ibaraki, 1979-1980.

2) F.W.Comer, F.McCapra, I.H.Qureshi, and A.I.Scott, Tetrahedron, 23, 4761 (1967).

3) (a) H.Hashimoto, K.Tsuzuki, F.Sakan, H.Shirahama, and T.Matsumoto, Tetrahedron Lett., 3745 (1974); (b) B.M.Trost, C.D.Shuey, and F.DiNinno, J. Am. Chem. Soc., 101, 1284 (1979); (c) P.T.Lansbury, N.Y.Wang, and J.E.Rhodes, Tetrahedron Lett., 2053 (1972); (d) M.Yamazaki, M.Shibasaki, and S.Ikegami, Chemistry Lett., 1245 (1981).

4) The compound (2) can be readily obtained in large quantities from 1,3-cyclooctadiene, see J.K.Crandall and L.-H.Chang, J. Org. Chem., 32, 532 (1967).

5) Satisfactory spectroscopic data (mass spectrum, PMR, IR, etc.) were obtained for this substance.

6) Structures of the products were anticipated on the basis of the mechanism of asymmetric synthesis *via* chiral organoborane reagents, see H.C.Brown, P.K.Jadhav, and A.K.Mandal, Tetrahedron, 37, 3547 (1981).

7) Prepared by adding borane (0.96 M THF solution, 3.80 ml, 3.65 mM) to (-)-α-pinene (1.09 g, 8 mM), $[\alpha]_D^{25}$-47.5°(neat), at 0°C and stirring the mixture for 13 hr under the same conditions.

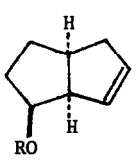
8) Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] europium(III) derivative was used.

9) Prepared efficiently from the alcohol (i)[6] by a series of reactions [(i) MEM chloride-(i-Pr)$_2$NEt, (ii) NBS-aqueous DMSO, (iii) Bu_3SnH, (iv) PCC, (v) H_2SO_4-aqueous acetone].

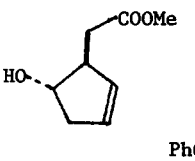
10) Optically pure 7 was synthesized from the known hydroxy-ester (ii), $[\alpha]_D^{25}$+136°(*c* 0.98, MeOH), 92% optical purity. Details will be reported in due course.

11) A series of reactions [(i) $NaBH_4$, (ii) MEM chloride-(i-Pr)$_2$NEt, (iii) H_2-Pd/C, (iv) Chugaev reaction] afforded the compound (iii), which was efficiently converted to (+)-7.[9]

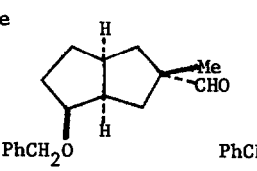
12) Structure of 9 was confirmed as follows. Protection of 9 as benzyl ether, followed by treatment with HCl in aqueous MeOH, produced the aldehyde (iv)[PMR($CDCl_3$) δ1.17 (3H,s)] without the concomitance of the stereoisomer. Likewise, the cyclopropane derivative obtained in *ca.* 0.7% yield afforded the aldehyde (v)[PMR($CDCl_3$) δ1.10 (3H,s)]. Undesired aldehyde (v) was cleanly converted to the lactone (vi) by a series of reactions [(i) Jones oxidation, (ii) CH_2N_2, (iii) H_2, Pd/C, (iv) H^+].



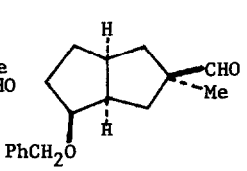
(±)-i: R=H
(-)-iii: R=MEM



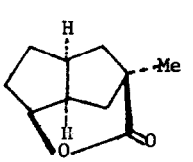
ii



iv



v



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