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1,2-CARBONYL TRANSPOSITION OF *cis*-BICYCLO[3.3.0]OCTAN-2-ONE TO ITS 3-ONE SKELETON: APPLICATION TO SYNTHESES OF *dl*-HIRSUTIC ACID AND *dl*-9(0)-METHANOPROSTACYCLIN

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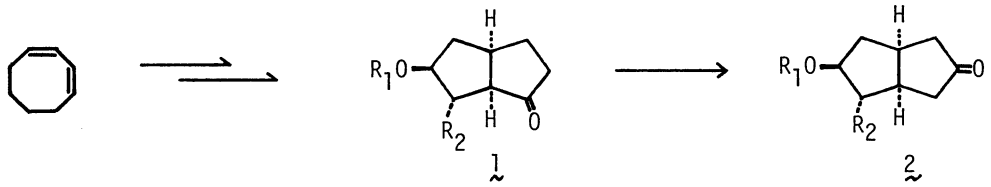
A synthetic route to dl-hirsutic acid and an improved synthesis of dl-9(0)-methanoprostacyclin, both of which employ the 1,2-carbonyl transposition as a key step, are described.

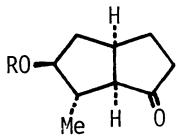
In the course of our synthetic studies on biologically interesting substances (coriolin and prostacyclin methano-analogs) by utilizing 1,3-cyclooctadiene,[1] we became interested in the development of a methodology of the 1,2-carbonyl transposition (1→2). Since a variety of ketones (1) are now available in the stereo and regiocontrolled manner starting from 1,3-cyclooctadiene,[1] the efficient transposition (1→2) opens new synthetic routes to other polycyclopentanoids such as hirsutic acid and hirsutene. In this communication, we describe a new synthesis of hirsutic acid and an improved synthesis of 9(0)-methanoprostacyclin, both of which employ the efficient 1,2-carbonyl transposition as a key step.



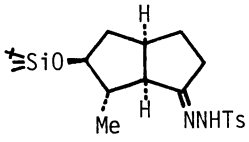
Several unsatisfactory trials of the 1,2-carbonyl transposition[2] (1→2) led us to the development of a new efficient method based on the steric nature of a *cis*-bicyclo[3.3.0]octane ring system. Thus, the ketone (3), obtainable in 9 steps from 1,3-cyclooctadiene,[1] was converted to the tosylhydrazone (4) by treatment with 1 equiv of tosylhydrazine in ethanol (reflux, 6 h), and the tosylhydrazone (4) was directly subjected to the Bamford-Stevens reaction (5 equiv of MeONa, diglyme, reflux, 1 h)[3] to afford the olefinic product (5)[4] in the regiocontrolled manner. Treatment of the crude reaction products with fluoride ion gave the hydroxy-olefin (6) in 51% yield from 3 [pmr($CDCl_3$,TMS): δ5.15-5.92 (2H, olefinic protons)], which was again protected as THP ether.[5] Reaction of the THP ether (7) with 1 equiv of NBS in DMSO-H_2O (100:1)(10.2 ml/g) at room temperature for 20 min yielded the bromohydrin (8)[6] as the major product, which was subsequently treated with 1.5 equiv of tri-*n*-butyltin hydride and a catalytic amount of AIBN in benzene (reflux, 10 min) to afford the alcohol (9) as the major product. Oxidation of 9 with PCC and sodium acetate in methylene chloride gave the transposed ketone (10) in 65% overall yield from 6 (*Rf* 0.48, silica gel, ether-petr.ether 2:1) and a small amount of 11 (*Rf* 0.58) in 6% yield.[7] The regio and stereocontrolled formation of 8 is rationalized by considering that the *exo*-bromonium ion was attacked by hydroxide ion at the less hindered site.[1c,8]

Having established an efficient synthesis of 10, the ketone (10) is now available in sufficient quantity to pursue our synthetic studies toward hirsutic acid.[9] The ketone (10) was

subjected to Wittig reaction ($Ph_3P=CH_2$, DMSO) to yield the *exo*-olefin (12) in quantitative yield. Treatment of 12 with methoxycarbene[9a] afforded a mixture of 13a and 13b (2.6:1) quantitatively. Deprotection of the desired 13a in AcOH-H_2O-THF (3:1:1) furnished the alcohol (14), which was then oxidized with PCC and sodium acetate in methylene chloride to give the ketone (15).[10] Treatment of 15 with aqueous methanolic hydrogen chloride at reflux temperature for 1.25 h yielded the aldehyde (16). Oxidation of 16 with Jones reagent and subsequent esterification with diazomethane resulted in the clean formation of the methyl ester (18) in 38% overall yield from 13a. The stereo and regiocontrolled introduction of an allyl group was performed by treatment of 18 with 10 equiv of allyl bromide and 1.5 equiv of sodium hydride in DME[9a,11] to give the ketone (19) in *ca.* 50% yield. The allyl-ketone (19) was subjected to Wacker-type oxidation by using palladium chloride[1e,1f,12] to afford the methyl-ketone (20) in 50% yield.[13] Cyclization of 20 by treatment with 0.5 equiv of potassium *t*-butoxide in *t*-butyl alcohol provided the tricyclic enone (21) in 53% yield, which is a key intermediate for the synthesis of hirsutic acid reported by Matsumoto and Shirahama.[9a] Comparison of its spectral data with those of an authentic sample confirmed their identity. Thus, a synthetic route to *dl*-hirsutic acid (22) from 1,3-cyclooctadiene was accomplished by utilizing the 1,2-carbonyl transposition (3→10) as a key step reaction.



3: R=Si≡
11: R=THP



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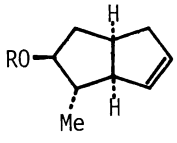
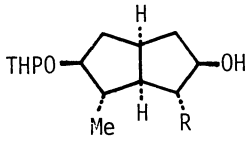
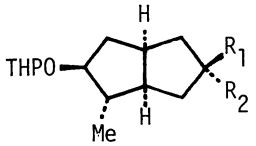


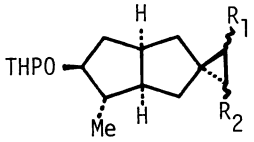
5: R=Si≡
6: R=H
7: R=THP



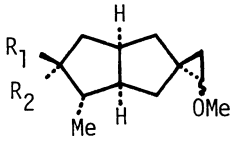
8: R=Br
9: R=H



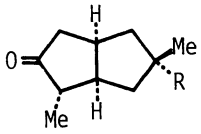
10: R_1-R_2=O
12: R_1-R_2=CH_2



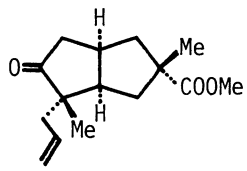
13a: R_1=H, R_2=OMe
13b: R_1=OMe, R_2=H



14: R_1=OH, R_2=H
15: R_1-R_2=O



16: R=CHO
17: R=COOH
18: R=COOMe



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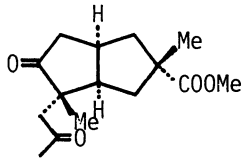

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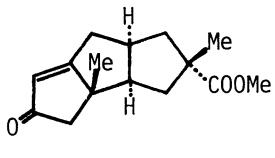

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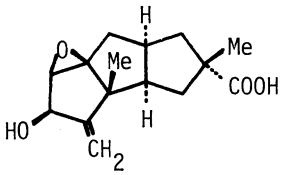
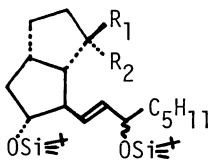


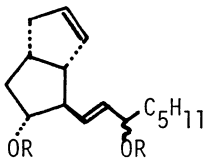
22

The 1,2-carbonyl transposition method developed above can be applied to the more complex molecule (23), whose synthesis from 1,3-cyclooctadiene has already been established in the stereo and regiocontrolled manner.[1] The ketone (23) was converted to 24 with 1 equiv of tosylhydrazine in ethanol (reflux, 6 h), which underwent the Shapiro reaction by treatment with 4 equiv of *n*-butyllithium in THF (-78°C, 1.25 h) to afford the olefinic product (25) in the regiocontrolled manner. Deprotection of 25 with fluoride ion gave the dihydroxy-olefin (26) in 57% yield from 23. At this stage, the isomers (C-15 position, PG numbering) were easily separable, and the 15α-isomer was again protected as THP ether to give the bis-THP ether (27) in quantitative yield. Treatment of 27 with 1 equiv of NBS in DMSO-H_2O (100:1)(5.1 ml/g)[6] at room temperature for 20 min afforded the bromohydrin (28) as the major product,[14] which was then subjected to reductive debromination by reaction with 1.5 equiv of tri-*n*-butyltin hydride and a catalytic amount of AIBN in benzene (reflux, 10 min) to provide the alcohol (29) as the major product. Oxidation of 29 with PCC and sodium acetate in methylene chloride resulted in the formation of the transposed ketone (30) and its isomer (31) in 84% overall yield from 27. Separation of the transposed ketone (30) from 31 was so difficult at this stage that a mixture of 30 and 31 was deprotected in AcOH-H_2O-THF (3:1:1) to give a easily separable mixture of 32 (*Rf* 0.14 silica gel, ether) and 33 (*Rf* 0.22) in a ratio of 5:1. The diol (32), synthesized above, was identical with an authentic material[1] in every respect (ir, pmr, mass, tlc). The present carbonyl transposition (23→32) offers an improved synthesis of biologically interesting 9(0)-methanoprostacyclin (34) from 1,3-cyclooctadiene.[15]



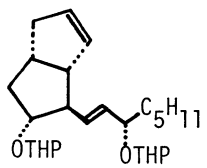
23: R_1-R_2=O

24: R_1-R_2=NNHTs



25: R=Si≡

26: R=H



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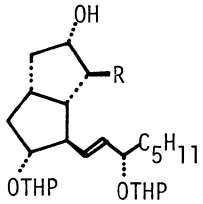
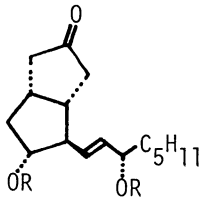


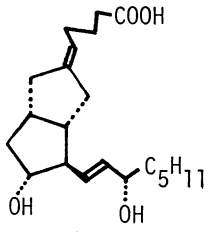
28: R=Br

29: R=H



30: R=THP

32: R=H



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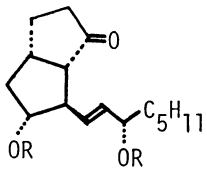

31: R=THP

33: R=H

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References

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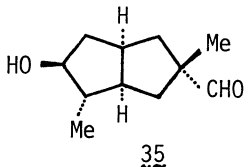
2) For recent excellent publications discussing about 1,2-carbonyl transposition studies, see W.E.Fristad, T.R.Bailey, and L.A.Paquette, J. Org. Chem., 43, 1620 (1978); Y.K.Yee and A.G.Schultz, ibid., 44, 719 (1979).
3) R.H.Shapiro, Organic Reactions, 23, 405 (1976).
4) A portion of the product (5) was deprotected under the reaction conditions used to give the hydroxy-olefin (6).
5) It is reported that the *t*-butyldimethylsilyl ether is usually cleaved by the use of NBS, see R.J.Batten, A.J.Dixon, and R.J.K.Taylor, Synthesis, 1980, 234.
6) Since the bromohydrins (8 and 28) are rather unstable under acidic conditions, the reaction should be quenched directly by the addition of saturated aqueous $NaHCO_3$ solution.
7) The ketones (11 and 33) can be recycled to the 1,2-carbonyl transposition reaction.
8) G.Stork and M.Isobe, J. Am. Chem. Soc., 97, 4745 (1975).
9) For previous total synthetic efforts with hirsutic acid, see a, F.Sakan, H.Hashimoto, A.Ichihara, H.Shirahama, and T.Matsumoto, Tetrahedron Lett., 1971, 3703; H.Hashimoto, K.Tsuzuki, F.Sakan, H.Shirahama, and T.Matsumoto, ibid., 1974, 3745; b, B.M.Trost, C.D.Shuey, and F.DiNinno,Jr., J. Am. Chem. Soc., 101, 1284 (1979); c, P.T.Lansbury, N.Y.Wang, and J.E.Rhodes, Tetrahedron Lett., 1972, 2053.
10) Attempts to cleave the cyclopropane ring of 13a with concomitant deprotection of the THP ether afforded the desired product (35) only in unsatisfactory yield.
11) S.Nozoe, J.Furukawa, U.Sankawa, and S.Shibata, Tetrahedron Lett., 1976, 195.
12) J.Tsuji, I.Shimizu, and K.Yamamoto, ibid., 1976, 2975.
13) In addition to 20, a small amount of the isomerized olefin (36) was formed.
14) Unreactivity of the ω-chain olefin might be ascribed to the steric hindrance around it.
15) Transformation of 32 to 9(0)-methanoprostacyclin (34) was already accomplished, see Ref. 1a.



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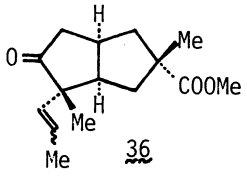

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