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SKELETAL REARRANGEMENTS OF TRICYCLO[6.3.0.0^{1,6}]UNDECAN-5-OLS TO FUNCTIONALIZED TRICYCLO[6.3.0.0^{1,5}]- and [5.3.1.0^{1,5}]UNDECANES

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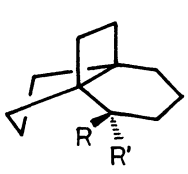
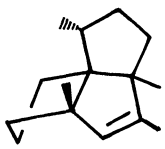
The functionalized tricyclo[6.3.0.0^{1,5}]- and [5.3.1.0^{1,5}]-undecanes are newly synthesized from endo- and exo-tricyclo-[6.3.0.0^{1,6}]undecan-5-ols by skeletal rearrangements using the solvolyses of their tosylates. Furthermore, a novel biologically active compound is derived readily from the rearrangement products.

Recently, much attention has been focused on polyquinane chemistry, because a lot of natural products possess the intriguing basic frameworks which featured mutually fused cyclopentane rings and some of them display significant biological activities.[1] In our previous report,[2] we have described a new synthetic approach to the basic carbon skeletons of some di- and triquinane sesquiterpenes by high-selective and stepwise skeletal rearrangements of exo- and endo-[4.3.2]-propellanols (1x and 1n). Furthermore, this rearrangement approach can be extended to the different 6-4-5 ring systems from the propellanes 1x and 1n. From the above point of view, we now wish to report here the skeletal rearrangements of endo- and exo-tricyclo[6.3.0.0^{1,6}]undecan-5-ols (5n and 5x) in order to obtain the functionalized tricyclo[6.3.0.0^{1,5}]- and [5.3.1.0^{1,5}]undecanes 8-11 which are the basic skeletons of isocomene (2)[3] and α-cedrene (3)[4] type polyquinane terpenoids, respectively. In addition, a preliminary result on the biological activities of the novel α-methylenecyclopentanone derivative 17 obtained easily from the rearrangement products 8-10 is reported.



1x R=OH, R'=H
1n R=H, R'=OH



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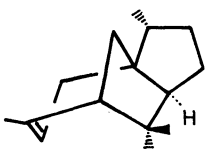

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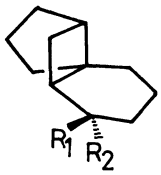
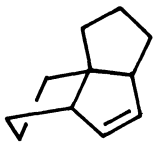


4 R_1, R_2=O
5n R_1=OH, R_2=H
5x R_1=H, R_2=OH
6 R_1=H, R_2=OCOPh
7n R_1=OTs, R_2=H
7x R_1=H, R_2=OTs

The endo and exo alcohols 5n[5,6] and 5x[5] were prepared in an approximate 11 : 1 ratio by reduction of the parent ketone 4[8] with lithium aluminum hydride (LAH) [Et_2O, rt, 84%]. Alternatively, the exo alcohol 5x was derived from 5n by inversion[9] of the hydroxyl group using Mitsunobu reaction [$(EtO_2CN)_2$, PPh_3, $PhCO_2H$, THF, rt, 52%] followed by alkaline hydrolysis of the benzoate 6 [KOH, MeOH, 65 °C, 91%]. Since the acid-catalyzed rearrangements of 5n and 5x did not occur under the conditions similar to the cases of the propellanols 1x and 1n,[2] the alcohols were converted into the corresponding tosylates 7n[5] and 7x[5] [tosyl chloride (TsCl), Py, 0 °C, 97% for 7n; TsCl, NaH, THF, rt, quantit. for 7x] for submitting to the solvolytic rearrangement.

Acetolysis of the endo tosylate 7n [AcONa, AcOH, 118 °C] followed by LAH reduction of the crude reactant predominantly gave isocomene type compounds 8[5] (28%), 9[5] (24%), and 10[5] (3%), along with α-cedrene type compound 11[5] (18%).[10] On the other hand, the similar treatment of the exo tosylate 7x afforded 11 (31%) as a major rearranged product together with 8 (2%) and 9 (trace).[10]



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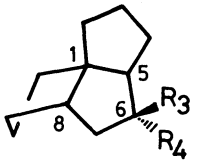
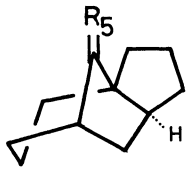
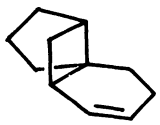


9 R_3=H, R_4=OH
10 R_3=OH, R_4=H
13 R_3=R_4=H



11 R_5=H, OH
14 R_5=O
15 R_5=H_2



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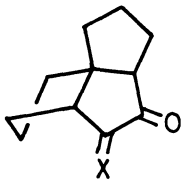
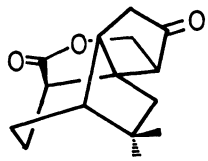


16 X=H_2
17 X=CH_2



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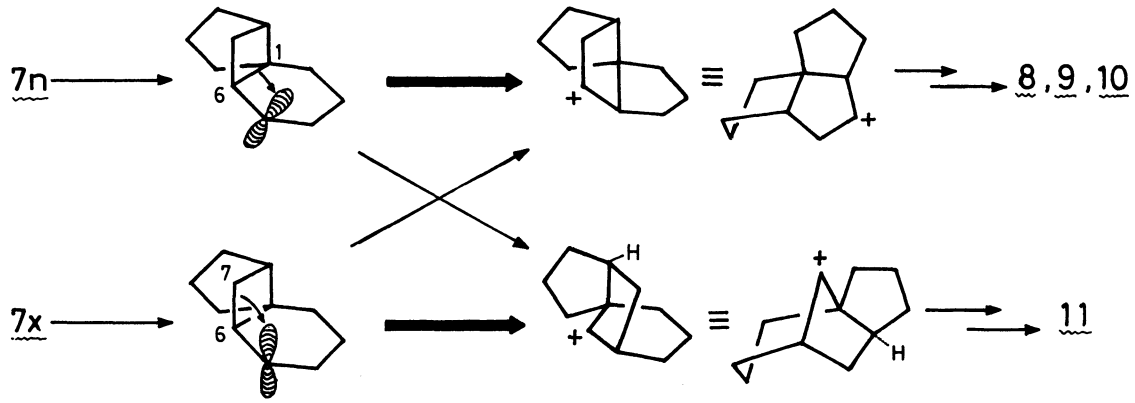
Since hydrogenation of the symmetrical (6 signals in ^{13}C NMR spectrum) olefin 8 [H_2, Pd/C, AcOEt, rt, quantit.] gave the known hydrocarbon, cis,cis-tricyclo-[6.3.0.$0^{1,5}$]undecane (13),[12] the structure of 8 was confirmed as the 6-ene derivative. Hydroboration-oxidation of 8 [B_2H_6, THF, rt, then H_2O_2, NaOH] furnished the alcohols 9 (58%) and 10 (17%), indicating that 9 and 10 have the same skeleton as that of 8 and are the 6-ol derivatives. Furthermore, the stereochemistry of the hydroxyl groups of them was determined by comparison of their ^{13}C NMR chemical shifts with the calculated values[13] based on those of bicyclo[3.3.0]octane derivatives.[14] Collins oxidation of the alcohol 11 [CrO_3-Py_2, CH_2Cl_2, rt, 92%] afforded the ketone 14[5] which showed an IR absorption at 1740 cm^{-1} due to hindered cyclopentanone. Wolff-Kishner reduction of 14 [N_2H_4, KOH, ethyleneglycol, 200 °C, 64%] yielded the known hydrocarbon, tricyclo[5.3.1.$0^{1,5}$]undecane (15),[12] and, therefore, the structure of 11 was elucidated to be the 11-hydroxy α-cedrene type derivative.

Consequently, the skeletal rearrangements of endo- and exo-tricyclo-[6.3.0.$0^{1,6}$]undecan-5-yl tosylates (7n and 7x) preferentially proceeded in the manner similar to the cases of the propellanols 1x and 1n[2] to give the carbon frameworks of isocomene and α-cedrene type terpenoids. Namely, the C(1)-C(6) or C(6)-C(7) cyclobutane bond migrates preferentially as shown in Scheme 1, because of the stereoelectronic effect of the p-orbitals developed from the respective tosylates.



Scheme 1.

Moreover, for the purpose of the exploitation of novel biologically active substances, the isocomene type compounds 9 and 10 were transformed readily to the α-methylenecyclopentanone[15] derivative 17 by oxidation and subsequent α-methylenation of the resulting ketone 16. Interestingly, 17 exhibited higher cytotoxicity than the antibiotics, quadrone (18),[17] against tumor cells (P388, L1210, 3LL, and LY) of mice in vitro, and the detail will be shortly reported.

We would like to thank Dr. N. Ida and Mr. H. Koike of Basic Laboratories, Toray Industries, Inc. for the screening.

References

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2) K. Kakiuchi, T. Tsugaru, M. Takeda, I. Wakaki, Y. Tobe, and Y. Odaira, J. Org. Chem., 50, 488 (1985).
3) L. H. Zalkow, R. N. Harris, III, D. Van Derveer, and J. A. Bertrand, J. Chem. Soc., Chem. Commun., 1977, 456.
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5) All new compounds gave satisfactory spectral and analytical data except for tosylates 7x and 7n. Selected data are as follows:
5n: IR 3300, 1060, 1005 cm^{-1}; ^1H NMR (CCl_4) δ 1.0-2.4 (m, 17H), 3.68-3.92 (m, 1H).
5x: IR 3300, 1050, 1025, 990 cm^{-1}; ^1H NMR (CCl_4) δ 1.0-2.4 (m, 17H), 3.56-3.80 (m, 1H).

7n: IR 1595, 1350, 1170, 900 cm^{-1}; ^1H NMR (CCl_4) δ 1.0-2.3 (m, 16H), 2.41 (s, 3H), 4.50-4.76 (m, 1H), 7.24 (d, 2H), 7.67 (d, 2H).

7x: IR 1590, 1360, 1165, 800 cm^{-1}; ^1H NMR (CCl_4) δ 1.0-2.3 (m, 16H), 2.48 (s, 3H), 3.60-3.88 (m, 1H), 7.36 (d, 2H), 7.88 (d, 2H).

8: ^1H NMR (CCl_4) δ 1.1-1.9 (m, 12H), 2.60 (d, J = 8 Hz, 2H), 5.38 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 134.4 (d, 2C), 59.3 (s), 58.5 (d, 2C), 41.5 (t, 2C), 32.5 (t, 2C), 25.6 (t, 2C).

9: ^1H NMR (CCl_4) δ 1.1-2.2 (m, 16H), 2.76 (broad s, 1H), 3.50-3.76 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 79.4 (d, C-6), 60.1 (d, C-5), 60.0 (s, C-1), 48.2 (d, C-8), 42.4 (t), 42.2 (t, 2C), 32.8 (t), 30.6 (t), 26.2 (t), 25.8 (t).

10: ^1H NMR (CCl_4) δ 1.0-2.2 (m, 17H), 4.21 (q, 1H); ^{13}C NMR ($CDCl_3$) δ 74.6 (d, C-6), 60.9 (s, C-1), 55.6 (d, C-5), 47.9 (d, C-8), 42.3 (t), 41.5 (t), 41.2 (t), 34.5 (t), 27.4 (t), 27.0 (t), 25.8 (t).

11: ^1H NMR (CCl_4) δ 0.8-2.3 (m, 16H), 3.22 (s, 1H), 3.66 (d, J = 4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 76.9 (d), 53.0 (s), 45.1 (d), 41.8 (d), 35.6 (t), 35.0 (t), 32.9 (t), 30.1 (t), 26.6 (t), 23.5 (t), 19.7 (t).

12: ^1H NMR (CCl_4) δ 1.1-2.4 (m, 14H), 5.76-5.92 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 132.8 (d), 126.4 (d), 47.2 (s), 41.1 (t), 37.8 (d), 35.7 (d), 33.0 (t), 32.7 (t), 31.0 (t), 25.0 (t), 23.6 (t).

6) The stereochemistry of the hydroxyl groups was determined by comparison of IR absorption with that of bicyclo[4.2.0]octan-2-ols.[7]

7) A. C. Cope and R. W. Gleason, J. Am. Chem. Soc., 84, 1928 (1962).

8) Prepared readily by intramolecular photocycloaddition of the corresponding enone derived from 3-ethoxycyclohexenone and 4-pentenylmagnesium bromide. It was reported that the acid-catalyzed rearrangement of 4 in non-nucleophilic media gave tricyclo[3.3.3.0]undecan-2-one, see: R. L. Cargill, J. R. Dalton, S. O'Connor and D. G. Michels, Tetrahedron Lett., 1978, 4465.

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10) Unrearranged products 12,[5,11] 5n, and 5x were also obtained; from 7n, 12 (3%), 5n (4%), and 5x (3%): from 7x, 12 (3%), 5n (1%), and 5x (42%).

11) Also obtained from 4 by reaction with tosylhydrazide followed by treatment with MeLi.

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13) Characteristic values are as follows: (δ) 79.4 (C-6), 61.0 (C-5), 60.8 (C-1), 49.5 (C-8) for 9 and 74.8 (C-6), 61.5 (C-1), 55.6 (C-5), 47.1 (C-8) for 10.

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15) This moiety is well-known to be closely related to biological activities.[16]

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