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CONFORMATIONALLY SELECTIVE TRANSANNULAR CYCLIZATIONS OF HUMULENE 9,10-EPOXIDE. SYNTHESIS OF THE TWO SKELETALLY DIFFERENT CYCLOHUMULANOIDS: DL-BICYCLOHUMULENONE AND DL-AFRICANOL

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Summary —— Two cyclohumulanoids, dl-bicyclohumulenone (**4**) and dl-africanol (**7**) were synthesized *through newly developed conformationally selective transannular cyclization of humulene 9,10-*epoxide (**2**). The epoxide **2** was converted to a bicyclohumulenediol diacetate **3a** in 70% yield by *treatment with* $BF_3\cdot OEt_2$-Ac_2O, *while treatment of* **2** *with trimethylsilyl trifluoromethansulfonate* gave an africen-10-ol (**5a** and **5b**) in 80% yield. The two intermediates **3a** and **5a** furnished the natural products **4** and **7** in 30 and 8 % yield from **2** respectively.

Previously we reported[1] that humulene (**1**) is in equilibrium with its two stable CT and CC conformers and suggested that illudoids[2] and hirsutanoids might be biosynthetically derived from the CT and CC conformers respectively.[1] If one of the two stable conformers at *equilibrium can be selectively converted to the corresponding biosynthetically derived* cyclization products,[3] the process will make our simulation of cyclohumulanoid biosynthesis[4] *complete. Moreover, cyclization of a designated conformer* *via* *a conformationally selective* transannular cyclization constitutes a new strategy in synthetic organic chemistry.

Most cyclohumulanoids are considered to stem from 9,10-dihydrohumulen-9-yl cation.[5] However, selective protonation of the 9,10-double bond of humulene is so difficult[6] that we have attempted generation of the cation by cleavage of the epoxide ring of humulene 9,10-epoxide (**2**).[7] Since stable conformations of humulene epoxides are known to be very similar to those of the original olefin,[8] epoxide **2** undoubtedly exists as a mixture of CT and CC conformations at equilibrium.

The epoxide **2** upon treatment with $BF_3\cdot OEt_2$ (0.8 eq) in Ac_2O at -50° followed by 1 hr at -20 °C gave rise to bicyclohumulenediol diacetate **3a**[9] (mp 140-2°) in 70% yield. X-ray crystalographic analysis[10] revealed the configuration of **3a** which originates from the CC conformer of **2**. A computer generated perspective view of **3a** is shown in Fig 1. Transannular cyclization of the CC conformer was therefore selectively achieved. Selective hydrolysis of the 6-acetoxyl group was easily performed by refluxing with Na_2CO_3 (1.1 eq) in MeOH-water to afford **3b**[9] (mp 126-7°) in 99% yield. Silylation ($^tBuMe_2SiCl$, imidazole) and reduction ($LiAlH_4$ THF, rt, 1 hr) of **3b** gave **3c**[9] (mp 85-6°, 96%). Bromide **3d**, obtained by treatment of **3c** with PBr_3 (in pyr, at 0°→rt), was unstable and therefore immediately converted by reduction with $LiEt_3BH$ (THF-ether, rt) into **3e**[9] (56% from **3c**). Demasking of **3e** ($nBu_4N^+F^-$, THF, rt, 24 hr;

3f[9]: mp 94-5°, 91%) followed by Collins oxidation yielded (±) bicyclohumulenone (4) (mp 73°, 88%, 30% from 2), whose nmr and ir spectra were superimposable with those of the natural product, isolated from Plagiochila acanthophylla subsp. japonica.[5f]

Another conformationally selective transannular cyclization of 2 was performed by treatment of 2 with trimethylsilyl trifluoromethanesulfonate[11] (1.3 eq) in toluene at -20°→-10° for 6 hr and subsequent desilylation with KF in MeOH at rt for 20 hr. A mixture of alcohols 5a and 5b was obtained in 80% yield.[12] The mixture was separated by $AgNO_3$ impregnated silica gel chromatography (5a/5b = 1/2). A combination of shift reagent and decoupling experiments at 60 MHz and NMR spectrum at 270 MHz[13] established the configuration of olefins 5a[14] and 5b, both of which must be derived from the CT conformer of 2. The olefinic alcohol 5a was treated with PBr_3 (Et_2O, rt, 10 hr) to give a bromide 5c which was reduced without purification under Birch conditions (Na-liq NH_3, -78°, 30 min) to furnish an olefin 5d in 86% yield from 5a. The olefin 5d was quantitatively converted to a pair of stereoisomeric epoxides 5e and 5f (mCPBA, CH_2Cl_2, -15°, 10 min) from which epoxide 5e (moving faster on tlc) was separated in 55% yield. Treatment of 5e with LDA afforded an allylic alcohol 6 in 68% yield. Finally the allylic alcohol was hydrogenated (PtO_2, AcOEt, 0°) to an alcohol 7 (mp 47∼8°, 92%, 8% from 2). Spectra of the synthetic alcohol 7 and the olefin 5d were superimposable respectively with those of natural products, africanol and africene, which were found in the marine animal, Lemnalia africana.[15]

In summary, two structually different cyclohumulanoids have thus been synthesized from humulene epoxide 2 via conformationally selective transannular cyclization reactions. Conformational selectivity of the reaction could be rationalized by the different stabilities of transition states depending upon the presence (2→3a) or the absence (2→5a) of a nucleophile in the reaction medium because the epoxide 2 was shown to have same conformation in both the solvents namely Ac_2O and toluene as revealed by the ^{13}C NMR spectral studies.

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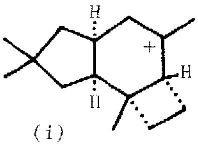
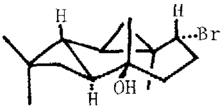
References and Notes

1) H.Shirahama, E.Osawa, T.Matsumoto, Tetrahedron Lett., 1987 (1978); J.Am.Chem.Soc.,102, 3208 (1980).

2) The group of sesquiterpenes biogenetically derived from humulene via the intermediate as protoilludyl cation (i) is refered to illudoids. [Y.Ohfune, H. Shirahama, T.Matsumoto, Tetrahedron Lett., 4377 (1975)]



(i)



(ii)

3) On treatment of humulene with NBS in aqueous acetone, there was obtained 3-hydroxy-6-bromo-tricyclohumulane (ii), whose conformation is known to be very similar to the original humulene CT conformer (X-ray analysis). (J.M.Greenwood, M.D.Solomon, J.K.Sutherland, A.Torre, J.Chem.Soc.,(C), 3004 (1968); F.H.Allen, D.Rogers, Chem.Commun., 582 (1966); 588 (1967); J.Chem. Soc.,(B), 1047 (1968)). To date, no compound with the conformation resembling the humulene CC conformer has been recognized.

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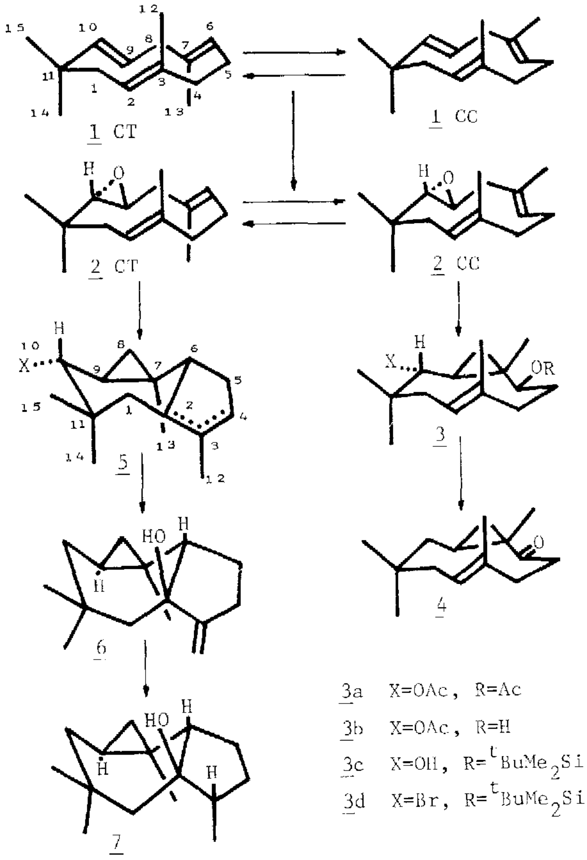
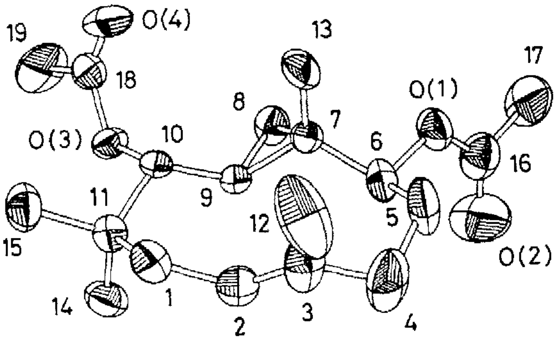
5) Cyclohumulanoids such as illudoid[a,2)], hirsutanoid[a,1)], Pentalenanoids,[b)] africanoid (africanol[c)] and oxysenoxyrene[d)]), and bicyclohumulenone,[f)] are all thought to originate from 9,10-dihydrohumulen-9-yl cation. (a) W.Parker, J.S.Roberts, R.Ramage, Quart.Rev. 21, 331 (1967). (b) D.E.Cane, T.Rossi, J.P.Pachlatko, Tetrahedron Lett., 3639 (1979); H.Seto, H.Yonehara, J.Antibiotics, 33, 92 (1980). (c) B.Tursh, J.C.Braekman, D.Daloze, P.Pritz, A. Kelecom, R.Karlsson, D.Losman, Tetrahedron Lett., 747 (1974). (d) Bohlmann[e)] described oxysenoxyrene originated from humulene 2,3-epoxide, however, biosynthesis from 9,10-epoxide along a similar path to our synthesis seems to give a more reasonable explanation. (e) F. Bohlmann, C.Zdero, Phytochem. 17, 1669 (1978). (f) A.Matsuo, H.Nozaki, M.Nakayama, Y.Kushi, S.Hayashi, T.Komori, N.Kamijo, J.Chem.Soc., Chem.Commun. 174 (1979).

6) Protonation of humulene has been extensively studied. In all cases, so far examined, attack by proton is always initiated at the 6,7-double bond. Y.Naya, Y.Hirose, Chem.Lett., 133 and



3a X=OAc, R=Ac
3b X=OAc, R=H
3c X=OH, R=^{t}BuMe$_2$Si
3d X=Br, R=^{t}BuMe$_2$Si

Fig 1 A perspective view of bicyclohumulenediol diacetate 3a (X-ray analysis)



3e X=H, R=^{t}BuMe$_2$Si
3f X=H, R=H

5a $\Delta^{2,3}$, X=OH
5b $\Delta^{3,4}$, X=OH
5c $\Delta^{2,3}$, X=Br
5d $\Delta^{2,3}$, X=H
5e β-2,3-epoxy-, X=H
5f α-2,3-epoxy-, X=H

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7) A.Sattar, J.Forrester, M.Moir, J.S.Roberts, W.Parker, Tetrahedron Lett., 1403 (1976).

8) The conformation of humulene diepoxide is known to be very similar to that of humulene. M.E.Cradwick, P.D.Cradwick, G.A.Sim, J.Chem.Soc., Perkin II, 404 (1973).

9) Spectral data of all compounds are consistent with the structures depicted in the figure. NMR spectra were measured in $CDCl_3$ (3a, c, d, f) and in CCl_4 (5c, e, 6) and IR spectra were observed either in nujol or neat. NMR and IR spectral data are listed herein. 3a: IR 1722 cm^{-1}; NMR 0.12 (1H, dd, J=9.5, 4.5, 8-H), 0.63 (1H, dd, J=6, 4.5, 8-H), 0.91, 1.08, 1.14 (each 3H, s, Me×3), 1.68 (3H, bs, 12-Me), 1.99 (6H, s, Ac×2), 4.10 (1H, dd, J=9, 2.5, 6-H), 4.52 (1H, d, J=8, 10-H), 5.30 (1H, bd, J=10.5, 2-H). 3c: IR 3450 cm^{-1}; NMR 0.00 (6H, s, $SiMe_2$), 0.37 (1H, dd, J=9.5, 4.5, 8-H), 0.50 (1H, dd, J=12, 4.5, 8-H), 0.87 (9H, s, ^tBuSi), 0.94 (3H, s, 13-Me), 1.04 (6H, s, Me×2), 1.63 (3H, bs, 12-Me), 2.71 (1H, dd, J=9, 3, 6-H), 2.93 (1H, bd, J=7.5, 10-H), 5.21 (1H, dd, J=10.5, 3, 2-H). 3d: NMR 0.00 (6H, s, $SiMe_2$), 0.59 (1H, t, J=5, 8-H), 0.86 (9H, s, ^tBuSi), 1.00 (3H, s, 13-Me), 1.20 (3H, s, Me), 1.28 (3H, s, Me), 1.64 (3H, bs, 12-Me), 2.73 (1H, m, 6-H), 4.03 (1H, d, J=8, 10-H), 5.2 (1H, m, 2-H). 3f: IR 3270 cm^{-1}; NMR -0.17 (1H, dd, J=4.5, 2.5, 8-H), 0.72 (1H, dd, J=4.5, 3.5, 8-H), 0.91, 0.95, 1.11 (each 3H, s, Me×3), 1.66 (3H, bs, 12-Me), 2.74 (1H, dd, J=8, 4, 6-H), 5.32 (1H, d, J=10.5, 2-H). 5c: NMR 0.3∼0.8 (3H, m, 8-H_2, 9-H), 0.88 (3H, s, 13-Me), 1.04 (6H, s, Mex2), 1.63 (3H, bs, 12-Me), 3.74 (1H, d, J=10, 10-H), 5e: NMR 0.05∼0.7 (3H, m, 8-H_2, 9-H), 0.87, 0.98, 1.02, 1.26 (each 3H, s, Me×4). 6: NMR 0.0∼0.7 (3H, m, 8-H_2, 9-H), 0.81, 0.98, 1.13, (each 3H, s, Me×3), 4.75 (1H, t J=2.5, 12-H), 4.95 (1H, t, J=2.5, 12-H).

10) Details of the analysis will be described elsewhere.

11) S.Murata, M.Suzuki, R.Noyori, J.Am.Chem.Soc., 101, 2738 (1979).

12) Treatment of 2 with $BF_3 \cdot OEt_2$ in ether leads to the formation of a similar mixture of the alcohols 5a and 5b(1:1) in 70% yield. J.A.Mlotkiewicz, J.Murray-Rust, P.Murray-Rust, W.Parker, F.G.Riddall, J.S.Roberts, A.Sattar, Tetrahedron Lett., 3887 (1979).

13) 5b: LIS ($Eu(fod)_3$) S-values 18.78 (15-Me), 18.07 (9αH), 10.96 (14-Me), 9.54 (8αH), 6.29 (8βH), 5.28 (13-Me), 2.95 (12-Me). NMR (270 MHz) 0.43 (1H, t, J=4.5, 8βH), 0.59 (1H, ddd, J=8.5, 8, 4.5, 9αH), 0.74 (1H, dd, J=8, 4.5, 8αH), 0.91 (1H, t, J=13, 1βH), 1.0 (3H, s, Me), 1.01 (6H, s, Me×2), 1.38 (1H, q, J=9.3, 6βH), 1.61 (3H, q, J=1.3, 12-Me), 1.75 (1H, dd, J=13.5, 3, 1αH), 2.11 (1H, m, 5βH), 2.28 (1H, ddq, J=15, 9.3, 2.5, 5αH), 2.56 (1H, m, 2αH), 3.18 (1H, d, J=8.5, 10βH), 5.28 (1H, bs, 4-H).

14) Recently Roberts and his coworkers reported the synthesis of 8-oxysenoxyri-4-en-3-one[5e] from the epoxide 2 via 5a, whose configuration was determined by X-ray analysis. (I.Bryson, J.A.Mlotkiewics, J.S.Roberts, Tetrahedron Lett., 3891 (1979). The spectral data of our compounds 5a and 5b were identical with those of their products.

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16) Address to which correpondence concerning the study should be sent.

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