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NEW TRICYCLIC KETONES DERIVED FROM EUDESMANOLIDE

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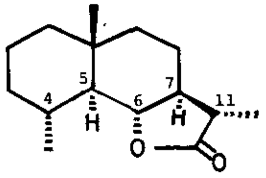
Abstract——The complete structures of new tricyclic keto olefins (4a,b) formed by cyclization-skeletal rearrangement of an eudesmanolide (1) with phosphoryl chloride were established by spectroscopic and X-ray crystallographic analyses of an unusual diol (6a), epoxy ketones (7a,b) and α,β-unsaturated ketones (8a,b).

In our continuing investigation of the cyclization-rearrangement of 3-deoxy-4β, 5αH-hexahydro-(-)-α-santonin(1) as a representative eudesmanolide with hot phosphoryl chloride, we obtained an optically active tetracyclic ketone, (-)-2,5,9-trimethyltetracyclo[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecan-11-one (2)[2] and a fragrant tricyclic ketone, (+)-1β,3α,6αH-4α,7β,11-trimethyltricyclo[5.4.$1^{3,6}$.$0^{1,7}$]dodec-10-en-5-one (3).[3] We now describe the structure determination of new tricyclic ketones (4a,b), which were first isolated in a pure state using this reaction followed by a different after-treatment from that used in previous cases,[2,3] as well as their derivatives such as an unusual diol olefin (6a), epoxy ketones (7a,b) and α,β-unsaturated ketones (8a,b). The dried sodio salt of the hydroxy acid prepared from



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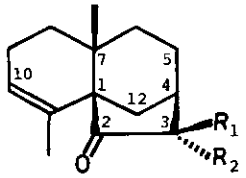
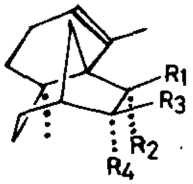


4a: R_1=H, R_2=CH_3, 7a: 4a (10α,11α-epoxy)
4b: R_1=CH_3, R_2=H, 7b: 4b (10α,11α-epoxy)



5a R_1=H, R_2=OH, R_3=CH_3, R_4=H
5b R_1=OH, R_2=R_3=H, R_4=CH_3
6a R_1=H, R_2=R_3=OH, R_4=CH_3
6b R_1=H, R_2=OH, R_3=OAc, R_4=CH_3
6c R_1=H, R_2=R_3=OAc, R_4=CH_3

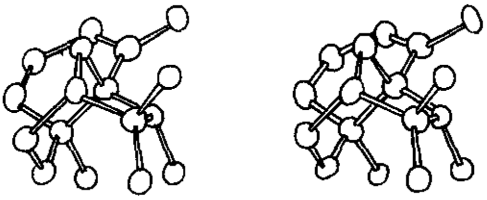
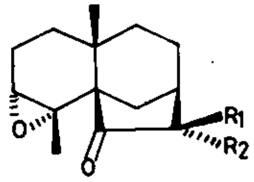
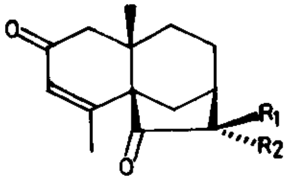


Fig. 1 Stereoview of 6a

1 was heated with $POCl_3$ as before.[2,3] After the reaction mixture was poured into hot water, a dark violet mass precipitated and was collected by washing it with MeOH. A dark colored oil obtained by evaporation of the combined MeOH solution was subjected to column chromatography on a silica gel column employing a gradient elution with n-hexane and ether to collect the new ketones (4a,b) (6.3%) accompanying 3 (2.0%) and 2 (1.7%). The main liquid product was shown gc-ms spectrometrically to be a mixture of ketone isomers (4a:4b/70:30), but no attempt to separate them using either usual or high pressure liquid chromatography was fruitful in our hands. Attention was then directed to the chemical modification of the ketones for easier separation. Reduction with $LiAlH_4$ in THF at ambient temperature overnight gave an oily mixture of alcohols (5a:5b/77:23) (45%)[4] together with an unusual crystalline diol (6a) (mp 133-134°C) (44%),[5] while $NaBH_4$ caused no reduction at all. When the alcohol portion except 6a was cautiously oxidized with Collins reagent, only a single major unreacted alcohol (5a) was separated from the ketones (4a,b). The compound (5a) was again oxidized with Jones reagent to yield the major ketone (4a) (mp 64-65°C) as the sole product.[6] The acetylation of 6a with Ac_2O and C_5H_5N at room temperature in the absence of DMAP (5 days) and in its presence (5 h) gave monoacetate (6b) and diacetate (6c), respectively. The difficulty in unequivocally determining the configuration of the hydroxyl groups led us to carry out direct X-ray crystallographic analysis with a single crystal of 6a. The crystal data are as follows: $(C_{15}H_{24}O_2)$ x 2, orthorhombic, mw= 236, $P2_12_12_1$, a= 18.925(9), b= 19.529(9), c= 7.265(4) Å, U= 2685 $Å^3$, Z= 8, Dc= 1.168 $g{\cdot}cm^{-3}$. The intensities of 1830 reflections were measured within 2θ= 130°. The crystal structure was solved by the direct method using MULTAN.[7] Refinement by the block-matrix least-squares method yielded the final R value of 0.096, without hydrogen atoms. The steroview of the molecular structure of 6a drawn by the ORTEP program is illustrated in Fig. 1. The unusual formation of 6a may presumably be attributed to the autooxidation of the relatively stable



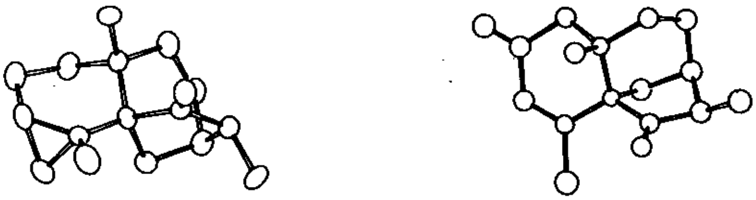
(7a) R_1=H, R_2=CH_3
(7b) R_1=CH_3, R_2=H



(8a) R_1=H, R_2=CH_3
(8b) R_1=CH_3, R_2=H

enolate (6d) of the sterically hindered ketone (4a),[8] on the basis of the observation that a small amount of 6a was obtained even in an oxygen free reaction condition.

On the other hand, a similar autooxidation was observed in the treatment of 4a,b with hot 15% NaOH for 8 h in an attempted epimerization.[2] When the oily crude material obtained was subjected to silica gel column chromatography, successive elutions with petroleum ether and ether afforded in poor yield 7a,b and 8a,b, respectively. The compound (7a) (mp 91-93°C) was successfully separated from 7b (mp 89-91°C) using a reversed phase HPLC technique.[9] 7a: cd (n-hexane) [θ](nm) +1982(max) (303). rd (n-hexane) [ϕ] +872 (326), [ϕ] -2082 (276) [a= +29.5]. The separation of 8a and 8b was also achieved with HPLC.[10] 8a: mp 134-135°C, cd (MeOH) [θ](nm) +35897 (255), -15432 (315). rd (MeOH) [θ](nm) +39227 (268), -8406 (332) [a= -476]. 8b: mp 110 -111°C, cd (MeOH) [θ](nm) +37515 (256), -17097 (310). rd (MeOH) [Φ](nm) +45772 (269), -6539 (327) [a= -523]. Since no appreciable differences were seen between the spectral data of a pair of 7a and 7b as well as those of another pair of 8a and 8b, both 7a,b and 8a,b should be regarded as epimeric pairs of identical configuration with respect to C(3) as shown in their foumulae. Epoxidation of the epimeric mixture of 4a,b with buffered MCPBA gave 7a as the major product and 7b as a minor one, while oxidation with Collins reagent



(7a)　　(8b)

Fig. 2 Perspective views of 7a and 8b

yielded 8a as the major one and 8b as a minor one. Even though these chemical transformations confirm every structure of 7a,b and 8a,b assigned from the spectral data, a further rigorous foundation for the stereochemistry especially at C(3) was obtained by direct X-ray crystallographic analyses of 7a and 8b described below. Crystal data of 7a: $C_{15}H_{22}O_2$, mw 234.3, orthorhombic, space group $P2_12_12_1$, z= 4, Dc= 1.199 $g \cdot cm^{-3}$, a= 8.798(2), b= 18.929(4), c= 7.793(2) Å, U= 1298.2 $Å^3$. The intensities of 958 unique reflections out of 1278 theoretically possible ones within 2θ angle of 130° were measured with the 2σ(I) level. The crystal structure was also solved as described earlier (R_{final} = 0.096). The crystal data of 8b: $C_{15}H_{20}O_2$, mw 232.3, monoclinic, space group $P2_1$, a= 10.860(7), b= 8.193(6), c= 7.133(6) Å, β= 92.49(1)°, U=634.1 $Å^3$, z= 2, Dc= 1.217 $g \cdot cm^{-3}$. 910 Reflection (6°< 2θ <156°). R_{final} 0.087. Perspective views of molecular structures of 7a and 8b are shown in Fig. 2.

In conclusion, the structure of the current tricyclic ketone (4a), which has not as yet been isolated in pure form,[2,3] has now been unambiguously determined. The formulae of 4a and 4b including their absolute configurations, i.e. (+)-4αH-3α,7β,11- and (+)-4αH-3β,7β,11-trimethyltricyclo$[5.4.1^{1,4}.0^{1,7}]$dodeca-10-en-2-one, are established on the basis of the complete structure of the epoxy derivative (7a), i.e. (+)-4αH-10α,11α-epoxy-3α,7β,11β-trimethyltricyclo$[5.4.1^{1,4}.0^{1,7}]$dodecan-2-one deduced from the X-ray analysis and cd/rd determinations mentioned above. The absolute configuration of 7a can be determined by the strong positive cd and rd Cotton effects consistent with that predicted from the octant sector diagram for 7a. An unexpected minor oxidation product (8b) separated in the alkaline treatment after the reaction of 1 with $POCl_3$, that is, the Collins oxidation product of 4a,b, revealed the 9-keto derivative of the minor epimeric ketone (4b) to be formulated as (-)-4αH-3β,7β,11-trimethytricyclo$[5.4.1^{1,4}.0^{1,7}]$dodeca-10-en-2,9-dione. Similarly the unusual olefin diol (6a) is expressed as (-)-4αH-3β,7β,11-trimethyltricyclo$[5.4.1^{1,4}.0^{1,7}]$dodeca-10-en-2β,3α-diol. In the equilibration under alkaline condition between the three pairs of epimers at C(3), 3α-methyl epimer i.e. 4a, 7a and 8a always predominates over the corresponding 3β-methyl ones, i.e. 4b, 7b and 8b, respectively.

Further studies on the autooxidation of 4a,b to the epoxy ketones (7a,b) and α,β-unsaturated ketones (8a,b) is now in progress. The reaction mechanism for the cyclization-skeletal rearrangement of the carbobicyclic lactone (1) *via* the present tricyclic ketones (4a,b) to the tetracyclic ketone (2) will be reported in comparison with the case of 3, which is the isomer of 4 possessing a different connection with respect to the C ring to be constructed on the B ring in the same A/B cis-octalin system with non-steroidal conformation.

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4. ^{1}H-nmr signal of C(2)-H in 5a and 5b appeared at 4.03 and 3.73 ppm as a doublet with spacing of 5 Hz, respectively.
5. ^{1}H-nmr signal at 1.54 ppm (2H, OH x 2, disappeared with the addition of D_2O) and CI (NH_3)-ms ion peak of M^+ 236 suggests the presence of two hydroxyl groups.
6. All new compounds exhibited satisfactory analytical and spectroscopic data (UV, ir, ^{1}H- and ^{13}C-nmr, rd and cd) consistent with the proposed structures.
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8. I. A. Kaye, M. Fieser, and L. F. Fieser, J. Am. Chem. Soc., 1955, **77**, 5936.
9. μBondapak C18, CH_3CN/H_2O(7/3), 1 ml/min, RI, Rt: 7a, 2.6 min; 7b, 5.8 min.
10. μPorasil, $CHCl_3$/n-hexane(7/3), 1 ml/min, RI, Rt: 8a, 9.4 min; 8b, 9.8 min.

The fractional atomic coordinates for **6a**, **7a** and **8b**.
The values are multiplied by 10^4.

NO (**6a**)	ATOM	X	Y	Z
1	C(1)	8623(4)	2812(5)	4900(17)
2	C(2)	8990(5)	3485(5)	5616(21)
3	C(3)	8508(5)	4062(5)	5882(19)
4	C(4)	7796(5)	4030(4)	5772(15)
5	C(5)	7439(4)	3373(3)	5118(12)
6	C(6)	7360(5)	3382(4)	2959(13)
7	C(7)	6859(5)	2811(4)	2562(13)
8	C(8)	7252(5)	2115(4)	2938(15)
9	C(9)	7519(4)	2078(4)	4952(14)
10	C(10)	7879(4)	2738(4)	5680(12)
11	C(11)	6255(5)	2947(4)	3954(13)
12	C(12)	6628(4)	3328(4)	5588(11)
13	C(13)	5784(5)	2324(5)	4463(15)
14	C(14)	7343(6)	4656(4)	6010(20)
15	C(15)	7952(5)	2663(5)	7821(14)
16	O(1)	6477(3)	3015(3)	7337(8)
17	O(2)	5817(3)	3453(3)	3025(10)
18	C(1')	8430(5)	-687(5)	2631(14)
19	C(2')	8720(6)	-1232(5)	3771(17)
20	C(3')	9486(6)	-1144(5)	4330(17)
21	C(4')	9882(5)	-573(4)	3955(15)
22	C(5')	9564(4)	-3(4)	2802(11)
23	C(6')	9723(4)	-137(4)	728(13)
24	C(7')	9526(4)	532(4)	-145(11)
25	C(8')	8724(4)	637(5)	-112(13)
26	C(9')	8431(4)	603(5)	1856(13)
27	C(10')	8744(4)	44(4)	3083(11)
28	C(11')	9943(4)	1058(4)	1039(12)
29	C(12')	9958(4)	691(4)	2986(12)
30	C(13')	9656(5)	1792(4)	986(15)
31	C(14')	10692(6)	-573(6)	4377(20)
32	C(15')	8541(5)	174(5)	5107(12)
33	O(1')	9749(3)	1136(3)	4490(8)
34	O(2')	10679(3)	1074(3)	508(9)

NO(**7a**)	ATOM	X	Y	Z
1	C(1)	8371(11)	8782(5)	6363(12)
2	C(2)	9505(11)	8421(5)	5066(13)
3	C(3)	11088(12)	8798(5)	5213(14)
4	C(4)	10854(12)	9348(5)	6694(15)
5	C(5)	11108(12)	9005(6)	8474(15)
6	C(6)	10249(12)	8303(6)	8693(15)
7	C(7)	8538(11)	8334(5)	8074(14)
8	C(8)	7566(14)	8675(6)	9457(14)
9	C(9)	5824(13)	8635(6)	8986(16)
10	C(10)	5505(12)	8795(6)	7102(17)
11	C(11)	6747(11)	8843(5)	5793(14)
12	C(12)	9146(11)	9518(5)	6531(15)
13	C(13)	11426(14)	9164(6)	3444(16)
14	C(14)	8012(13)	7555(5)	7757(15)
15	C(15)	6367(14)	8742(6)	3884(15)
16	O(1)	9228(8)	7942(4)	4116(10)
17	O(2)	6024(9)	9493(4)	6505(11)

NO(**8b**)	ATOM	X	Y	Z
1	C(1)	7318(5)	6341(0)	3453(8)
2	C(2)	6593(6)	7584(10)	2263(9)
3	C(3)	7417(7)	8984(11)	1788(11)
4	C(4)	8717(8)	8347(11)	2449(13)
5	C(5)	9293(7)	7238(13)	1068(12)
6	C(6)	8428(7)	5798(10)	469(10)
7	C(7)	7781(6)	4980(9)	2106(9)
8	C(8)	8610(6)	3808(11)	3226(10)
9	C(9)	7996(7)	3125(11)	4903(10)
10	C(10)	7036(7)	4094(12)	5767(10)
11	C(11)	6647(6)	5549(11)	5102(9)
12	C(12)	8433(7)	7406(13)	4215(10)
13	C(13)	7238(10)	9633(13)	-250(15)
14	C(14)	6696(7)	4007(11)	1208(11)
15	C(15)	5641(8)	6499(16)	5971(13)
16	O(1)	5502(5)	7470(9)	1780(8)
17	O(2)	8303(6)	1781(8)	5536(9)

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