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PHOTOCHEMICAL REARRANGEMENT APPROACH TO THE TOTAL SYNTHESIS OF (±)-PINGUISONE AND (±)-DEOXOPINGUISONE

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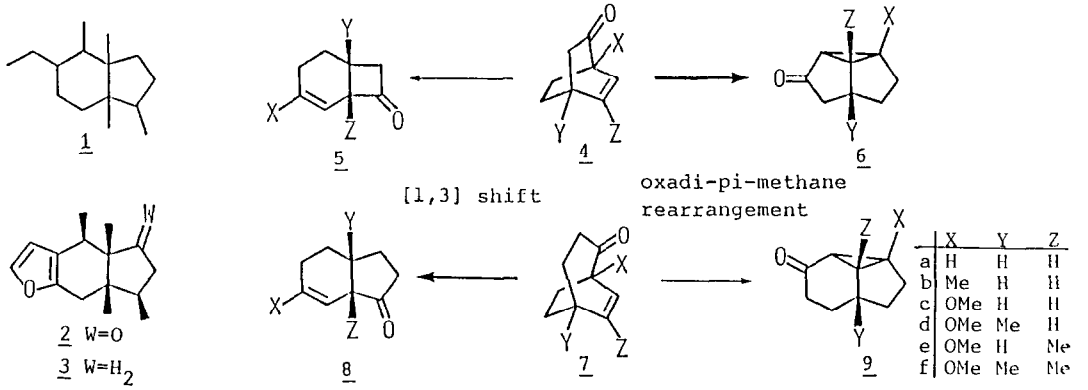
Summary: The total synthesis of (±)-pinguisone and (±)-deoxopinguisone, the unusual [5-6] fused-ring sesquiterpenes, was accomplished by the photochemical transformation of the bicyclo[3.2.2]non-6-en-2-one into the bicyclo[4.3.0]non-4-en-7-one.

Pinguisane-type sesquiterpenes, possessing the unusual terpene skeleton (1),[1] have been found from various kinds of liverworts; such as pinguisone (2)[2] from Aneura pinguis (L.) Dum.[2b] and deoxopinguisone (3)[3] from Ptilidium ciliare (L.) Nees.[3a] Those compounds are of particular interest in the total synthesis of natural products, because of their novel tricyclic furan skeletons with a cis-junction between the five- and six-membered rings and four adjacent cis-located methyl groups.[4] In connection with our program to develop methods for stereoselective syntheses of [m-n] fused-ring terpenoids from bridged bicyclic systems,[5] we have explored the photochemical reactions of bicyclo[3.2.2]non-6-en-2-ones (7). The photochemical behavior of bicyclo[2.2.2]oct-5-en-2-ones (4) has been examined extensively and the conversion into tricyclo[3.3.0.$0^{2,8}$]octan-3-ones (6), via the triplet-sensitized oxadi-pi-methane rearrangement (in acetone), has been applied to syntheses of natural products.[6] On the contrary, the photochemical rearrangement of the higher homologs (7) only has a precedent in the [1,3] sigmatropic shift of 7a into 8a.[7] Herein we report the point of the photochemical reactions and the application to the total synthesis of (±)-pinguisone and (±)-deoxopinguisone.



	X	Y	Z
a	H	H	H
b	Me	H	H
c	OMe	H	H
d	OMe	Me	H
e	OMe	H	Me
f	OMe	Me	Me

The Tieffeneau-Demjanov ring enlargement of 4b[8], 4c[9], and 4d[9] gave expected ketones 7b[10], 7c, and 7d, respectively, in good yields. When treated with trimethylsilyldiazomethane in the presence of BF_3 etherate,[12] compounds 4c, 4d, 4e,[11] and 4f underwent the ring expansion to give bicyclo[3.2.2]-nonenones 7c-7f, respectively, in more than 70% yields.

The results of the photochemical reactions of ketones 7a-7f, presented in Table 1, indicate that the preferential course is the [1,3] acyl migration to give the [5-6] cis-fused-ring system, except some reactions in acetone. The substrates which possess a methoxyl group at the C_1-position did not undergo the oxadi-pi-methane rearrangement. It is interesting from synthetic viewpoints that the products derived from 7c-7f have a masked carbonyl group in the six-membered ring and a ketone itself in the other ring.

Next, we applied this photochemical [1,3] rearrangement to the sesquiterpene synthesis outlined in Scheme 1. Bicyclo[2.2.2]octenone 11 was obtained as the major stereoisomer (ca. 10 : 1) in a range of 45% to 50% yields from the anisol (10) by sequential treatment with i) lithium (in ammonia),[13] ii) α-chloroacrylonitrile, and iii) potassium hydroxide and sodium sulfide.[9] That ^{1}H-NMR spectrum of 11 shows a doublet due to the C_8-methyl at δ=0.89, the 0.12 ppm upfield position in comparison with those of the minor stereoisomer, supports both of their stereostructures. The ring enlargement of 11[12] gave a mixture of 12 and its 3-trimethylsilyl derivative, and the mixture yielded pure 12 (79%) on desilylation. Photolysis of 12 in THF gave the desired ketone, 13 (59%).

After selective acetalyzation, 14 was transformed regioselectively into tetramethyl α,β-unsaturated ketone 16 (48% from 13). A dissolving metal reduction of 16 gave the alcohols, which were separeted into mixtures 17a (33%) and 17b (58%) by silica gel column chromatography. To confirm their C_9 stereochemistry, each of them was converted into the corresponding ketone. The ^{1}H-NMR spectrum of 18a shows the signals for the C_9-H at δ=3.04, more than 0.5 ppm

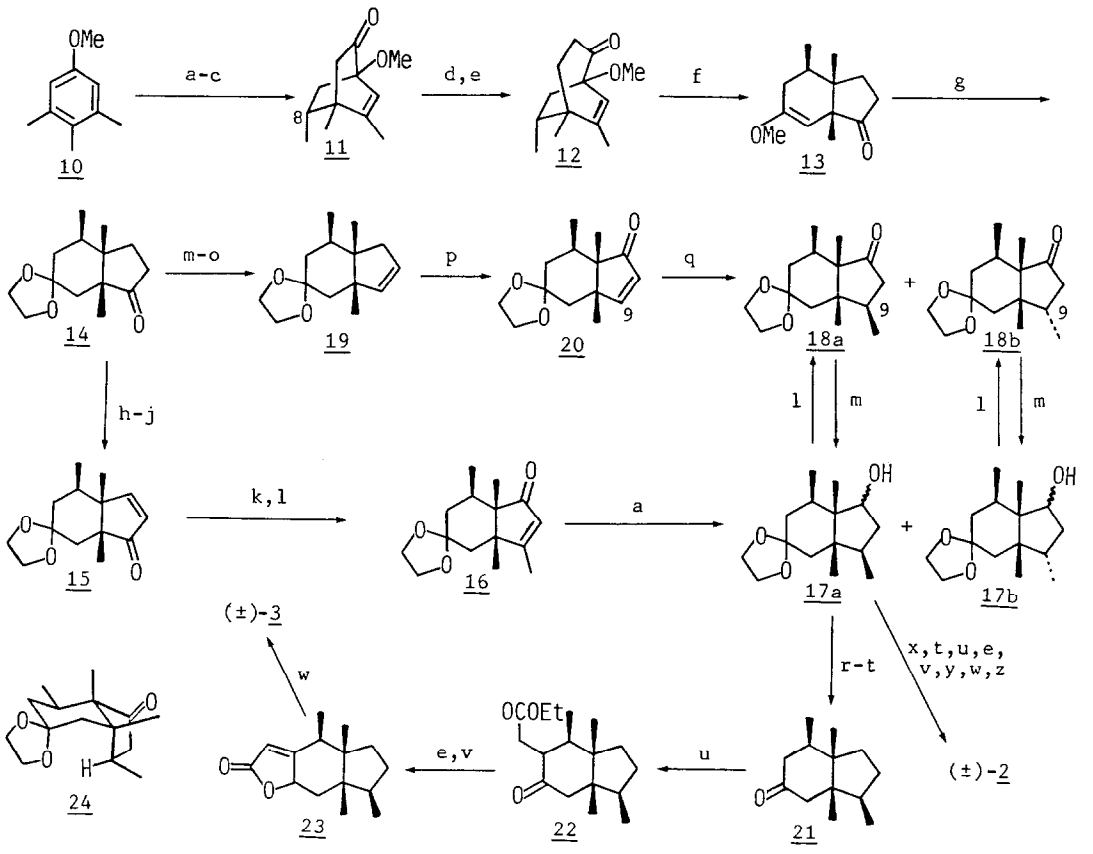
Table 1. Photochemical rearrangements of bicyclo[3.2.2]non-6-en-2-ones[a]

Substrate	Solvent	Time/h	Products, (yield, %)	Recov./%
7a	hexane	2	8a (53)	
7a	acetone	5.5	8a (37), 9a (18)	18
7b	hexane	3.5	8b (55)	
7b	acetone	3.5	8b (28), 9b (23)	17
7c	THF	4	8c (55)	
7d	hexane	6	8d (56)	8
7d	acetone	6	8d (41)	
7d	THF	4	8d (56)	
7e	THF	4	8e (47)	
7f	THF	4	8f (50)	

a) Carried out in a 0.01-0.05 M solution (ca. 100 ml) placed in an immersion well through Pyrex using a Riko 100 W high pressure mercury lamp under Ar.

lower than the resonances for that of 18b. This unusual low-field shift reflects that 18a has the depicted configuration and conformation (24) in which the C_9-H is close to the C_3-axial-oxygen.

This stereochemical outcome seemed to suggest that a methyl group is introduced from the less-hindered β-side at the C_9-position of α,β-unsaturated ketone 20. Thus we examined the other route to 17a. Ketone 14 was reduced by use of $LiAlH_4$ and then the major product, the α-alcohol (82%), was converted into 19 (95%). Oxidation of 19 with chromic anhydride·3,5-dimethylpyrazole complex[14] at -20 °C afforded an inseparable mixture of 20 and 15 in a ratio of 9 to 2 (79%). After treatment of this mixture with lithium dimethylcuprate at 0 °C, we could separate a mixture of 18a and 18b (76%) from the other products



Scheme 1. Total syntheses of (±)-pinguisone ((±)-2) and (±)-deoxopinguisone ((±)-3)[a]

a) (a) Li, NH_3, t-BuOH. (b) CH_2=C(CN)Cl, PhMe, 90 °C. (c) Na_2S, KOH, EtOH, H_2O. (d) $TMSCHN_2$, BF_3 ether, CH_2Cl_2. (e) K_2CO_3, MeOH, H_2O. (f) $h\nu$, THF. (g) 2-ethyl-2-methyl-1,3-dioxolane, TsOH, PhH. (h) LDA, $PhSSO_2Ph$. (i) $NaIO_4$, MeOH, H_2O. (j) PhMe, 90 °C. (k) MeLi, ether. (l) PCC, NaOAc, CH_2Cl_2. (m) $LiAlH_4$, ether. (n) MsCl, Py. (o) t-BuOK, DMSO. (p) CrO_3 3,5-DMP, CH_2Cl_2. (q) $(Me)_2CuLi$, ether. (r) NaH, CS_2, then MeI. (s) $(n\text{-Bu})_3SnH$, PhMe. (t) 1 M-HCl, acetone (1:4). (u) LDA, ICH_2CO_2Et, THF, HMPA. (v) TsOH, PhH. (w) DIBAH, THF, then 1 M-H_2SO_4. (x) NaH, $PhCH_2Br$, $(n\text{-Bu})_4NI$, DME. (y) BBr_3, CH_2Cl_2. (z) $(Ac)_2O$, DMSO.

by silica gel chromatography. Lithium aluminium hydride reduction of the mixture yielded 17a and 17b in 94% and 6% yields, respectively.

In order to prepare (±)-deoxopinguisone, the hydroxyl group of 17a was removed[15] (84%) and the 1,3-dioxolane was cleaved (97%). Keto-ester 22 was prepared regioselectively (63%). Hydrolysis followed by acid-catalyzed dehydration afforded butenolide 23 in 72% yield. DIBAH reduction and subsequent acid treatment gave the furan (69%) whose spectral chracteristics are identical with those of natural deoxopinguisone.

The hydroxyl group of 17a was protected as a benzyl ether[16] and then the 1,3-dioxolane was cleaved (84%). The butenolide was derived from the ketone (40%) in a manner similar to the conversion of 21 into 23. After cleaving the benzyl ether[17] (83%), DIBAH reduction gave the stereoisomeric furan-alcohols (66%). Dimethylsulfoxide-acid anhydride oxidation[18] of the alcohols gave (±)-2 (62%), also identical spectroscopically with natural pinguisone.

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