Tetrahedron Letters Vol.22, pp 409 - 412 0040-4038/81/0129-0409$02.00/0

SULFONE ROUTES TO STERICALLY HINDERED 7-CIS ISOMERS OF VITAMIN A. NEW GEOMETRIC ISOMERS OF VITAMIN A AND CAROTENOIDS 10.[1]

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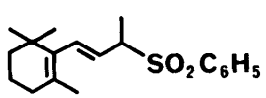
SUMMARY: A study examining the possible use of the C_{13} + C_7 and the C_{15} + C_5 routes with an intermediate C_{20}-sulfone to the hindered 7-cis isomers of vitamin A showed that the latter route is useful for preparation of the 7-cis and the 7-cis,13-cis isomers.

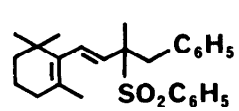
Following the publication of Julia on the preparation of vitamin A ester via sulfone intermediates[2] numerous papers appeared describing other sulfone routes to vitamin A,[3] carotenoids[4] and other related compounds.[5] These routes are attractive to us because of the potential application to the synthesis of the hindered 7-cis isomers, a subject of our recent interest.[1,6] In this paper we describe preliminary results on the C_{13} + C_7 and C_{15} + C_5 routes to the C_{20} system.

β-Ionyl sulfone (*trans*-I) was prepared according to the literature procedure.[3b] Sensitized irradiation under conditions for complete trans to cis isomerization[7] gave *cis*-I [^{1}H-nmr: H_7, 6.15 (d); H_8, 5.51 (dxd); H_9, 3.83 ppm (qxd); $J_{7,8}$ = 11.4; $J_{8,9}$ = 11.6 Hz]. Alkylation of *trans*-I with an allylic chloride was reported to proceed with retention of configuration at 7,8.[3b] This result however does not guarantee retention of configuration in the crowded cis sulfone during alkylation. We therefore first carried out exploratory reactions of both isomers of I with benzyl chloride.

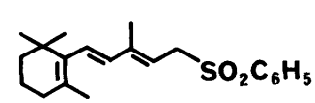
Reaction of *trans*-I in DMF with benzyl chloride in the presence of excess NaOH at 0-5° gave the expected tertiary *trans*-sulfone (II). However under the same conditions *cis*-I gave a mixture of approximately equal amounts of *trans*-I and *cis*-I. This result suggests that at this temperature range the loss of the cis geometry in the intermediate sulfone anion is competitive with its reaction with benzyl chloride. Indeed when the reaction temperature was lowered to -10° the product mixture contained predominantly *cis*-I. Compound *cis*-II is extremely crowded as revealed in its resistance toward base elimination[8] and its temperature dependent ^{1}H-nmr spectrum.[9]



I

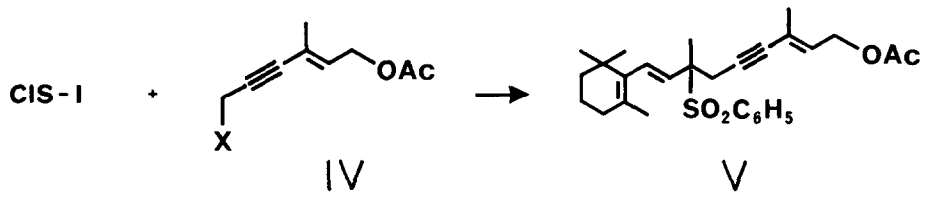


II



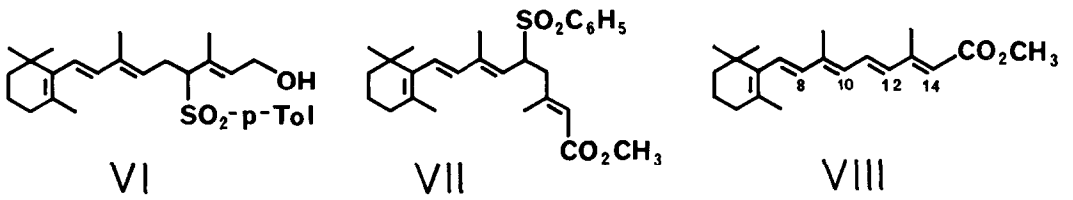
III

An attempt to alkylate *cis*-I with the C_7 acetate IV (X = Cl or Br) in order to prepare the C_{20}-sulfone (7-*cis*-V) was, however, unsuccessful. At -10°, no alkylation products were



detected; at temperatures (above 5°C) where alkylation proceeded at moderate rates, only 7-*trans*-V was isolated. Since sulfone V with a tertiary center at C_9 cannot be isomerized to the 7-cis isomer,[7b] this C_{13} + C_7 route has thus been shown not useful for preparation of 7-*cis*-vitamin A.

We next turned to the C_{15} + C_5 route. In a preliminary experiment, sulfone VI[3c] was irradiated in the presence of benzanthrone as sensitizer. A mixture of two isomeric sulfones was obtained. The ^{1}H-nmr spectrum is consistent only with those of the 7-cis (major) and 7-cis,9-cis (minor) isomers (see Table I). (The 13-trans geometry is not expected to change under the conditions of irradiation--see below.) Reaction of the sulfone with sodamide at



-30°[3a] did not result in elimination of sulfinic acid.[10] Other reported elimination conditions[3a] are not sufficiently mild to prevent the 7-cis triene of the product from undergoing cyclization.[11] Nevertheless the photochemical result is sufficiently encouraging for us to prepare the all-*trans*-sulfone VII[2] from C_{15}-sulfone III for further studies.

Under selective sensitization (benzanthrone as sensitizer), *trans*-VII gave, to our surprise, only the 7-cis isomer (for nmr data, see Table I). Reaction of the photoisomer with methanolic KOH gave primarily methyl 7-*cis*-retinoate (see experimental below). A weak doublet (δ 6.56 ppm, J = 12.2) due to H_8 of methyl 7-*cis*,9-*cis*-retinoate was also present. The extent (<10%) of loss of stereochemical integrity at the 9,10 double bond is about the same as in the elimination of the all-trans acetate of VII.[3a] Expectedly the stereochemistry around the 13,14 double bond was unaffected throughout the reaction sequence. Similarly, we have selectively photoisomerized 13-*cis*-VII to 7-*cis*,13-*cis*-VII which upon reaction with methanolic KOH gave 7-*cis*,13-*cis*-retinoate.

The high stereoselectivity clearly makes the current method more suitable for larger scale synthesis of the hindered 7-cis isomers than the non-stereoselective methods described earlier.[6,7a] For latter cases isomers of the final products were isolable only by high pressure lc. Also, since the retinoate ester have been converted to 7-cis retinols or

retinals without any loss of geometrical integrity,[6] the above method is useful for preparation of such analogs. Possible extension of the current study to preparation of new isomers in the A_2 series is being examined. Also, we are carrying out experiments designed to provide a better understanding of the controlling factors that led to the regio-specific photosensitized isomerization of VII.

PREPARATION OF METHYL 7-*CIS*-RETINOATE

To a solution of 1.81 ml (12.9 mmol) of $(i\text{-}Pr)_2NH$ in 10 ml dry THF was added 7.90 ml of n-BuLi (1.6 M in hexane). After stirring at r.t. for 20 min, it was cooled to -78° and 3.10 g (9.01 mmol) of C_{15}-sulfone II in 10 ml dry THF was added. The deep rose-red solution was stirred for 30 min, 1.78 g (9.22 mmol) of the *trans* isomer of methyl 4-bromo-3-methyl-2-butenoate[12] in 10 ml dry THF was added. After 5 h at -78°, the reaction was quenched by addition to 100 ml of 5% NH_4Cl. The product was extracted with 125 ml ether. The ether layer was washed with 100 ml 5% NH_4Cl, 2 x 100 ml H_2O, 2 x 50 ml sat. NaCl, dried with $MgSO_4$. Upon evaporation of solvent 5.11 g of an orange oil was obtained.

Purification was accomplished by two passes through a medium pressure lc column (silica gel column with 20% acetone in hexane) then recrystallized twice from 10% aqueous MeOH, yielding 2.30 g of colorless flat needles (m.p. 117-120°, 56% yield).

A solution of 0.68 g (1.48 mmol) of the above C_{20}-sulfone and 0.03 g (0.15 mmol) of benzanthrone in 20 ml of benzene was flushed with N_2 for 10 min. The flask was fitted with a septum and irradiated for 20 h with a 550 W Hanovia Hg lamp using a 3-74 Corning glass filter. The benzene was removed *in vacuo* and the brown residue was chromatographed twice (silica gel with 20% ether in hexane), yielding 0.53 g (1.17 mmol, 78%) of 7-*cis*-C_{20}-sulfone VII.

A solution of 110 mg (1.96 mmol) of KOH and 38 mg (0.08 mmol) of the above sulfone in 20 ml of MeOH was stirred overnight at r.t. Usual work-up involving extraction with ether, washing with H_2O, sat. NaCl solution and drying over $MgSO_4$ and evaporation of ether yielded 18.7 mg of a pale yellow powder (72% yield) which was shown by ^1H-nmr to be methyl 7-*cis*-retinoate in better than 90% isomeric purity (the remaining being the 7-cis,9-cis isomer).

ACKNOWLEDGMENT: This work was supported by a grant from the Public Health Services (AM-17806) We are grateful for the following gift samples of compounds used in this study: C_{15}-sulfone III from Dr. J. Decor of Rhône-Poulenc and vinyl-β-ionol and sulfone VI respectively from Dr. D. Andrews and Dr. G. Olson of Hoffmann-La Roche Inc.

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8. Refluxing methanol solution of NaOH (1 hr) or lithium cyclohexylamide in THF.

9. The room temperature spectrum is that of the diastereomeric rotamers frozen about the 6-7 single bond with the methyls-1,1,5 appearing at an unusually high field (δ, -0.02 to 0.9 ppm). A space filling model of *cis*-II showed that in one diastereomer the diene moiety assumed an almost orthogonal conformation with the two phenyl groups directly above CH_3-5 and one of the CH_3-1,1. Additionally, three other pairs of signals show different chemical shifts. The Δδ's vary between 3.2-98 Hz. Since each pair has a different coalescence temperature, the pmr spectrum shows an extremely wide range of temperature dependence (60°-170°). For restricted rotation of other related compounds, see: V. Ramamurthy, T. T. Bopp and R. S. H. Liu, Tetrahedron Lett., 3915 (1972).

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Table I. Key ^{1}H-nmr Signals of Isomers of Sulfones VI-VII and Methyl Retinoate (VIII)[a]

Compound	CH_3-5	CH_3-9	CH_3-13	H_7	H_8	H_{10}	H_{11}	H_{12}	H_{14}	H_{15}	$J_{7,8}$
all-*trans*-VI[b]	1.68	1.60	1.71	5.96	5.89	5.37	2.78		5.07	4.05	17.2
7-*cis*-VI	1.41	1.61	1.66	5.70	5.86		2.76			4.05	12.5
7-*cis*,9-*cis*-VI	1.37	1.61	1.66	5.70	6.12		2.69				12.0
all-*trans*-VII	1.64	1.22	2.11	5.94	5.94	5.08	4.08	2.50 3.13	5.67	--	?
7-*cis*-VII	1.30	1.26	2.09	5.84	5.93	5.15	4.04	2.44 3.06	5.60	--	12.0
7-*cis*,13-*cis*-VII	1.30	1.30	1.83	5.83	5.93	5.26	4.34	3.17 3.21	5.69	--	13.0
all-*trans*-VIII[c]		2.01	2.36	6.27	6.11	6.13	6.99	6.27	5.79	--	16.4
7-*cis*-VIII	1.52	1.90	2.34	5.95	6.09	6.20	6.95	6.25	5.78	--	12.5
7-*cis*,13-*cis*-VIII	1.48	1.87	2.02	5.92	6.11	6.28	6.90	7.73	5.62	--	12.7

a. XL-100. $CDCl_3$. Chemical shift in δ, ppm; coupling constants in Hz. b. Data of G. L. Olson, H. C. Cheung, K. D. Morgan, C. Neukon and G. Saucy, J. Org. Chem., 41, 3287 (1976). c. Data of W. Vetter, G. Englert, N. Rigassi and U. Schwieter, p. 214 in "Carotenoids" ed. by O. Isler, Birkhäuser Verlag, 1971.

(Received in USA 8 August 1980)