Pergamon

Tetrahedron Letters, Vol. 38, No. 16, pp. 2841-2844, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00475-9

A Convenient Asymmetric Access to Triquinanic Compounds

C. Bintz-Giudicelli, O. Weymann (in part) and D. Uguen*

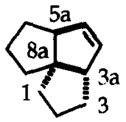
Laboratoire de Synthèse Organique, associé au CNRS; E.C.P.M-U.L.P.
1, rue Blaise Pascal; 67008 Strasbourg (France)

A. De Cian and J. Fischer

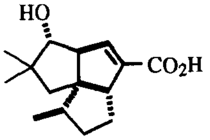
Laboratoire de Cristallochimie, associé au CNRS; U.L.P.
6, rue Blaise Pascal; 67070 Strasbourg (France)

Abstract: *Thermal rearrangement of a propargylic sulfinate prepared from* (R)*-pulegone led, with an acceptable diastereoselectivity, to a spiro sulfone which could be transformed into dihydropentalenic acid, methyl ester.* © 1997 Published by Elsevier Science Ltd.

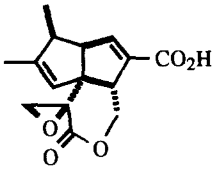
Pentalenic acid, **1**, is a natural compound biogenetically related to farnesyl pyrophosphate from which it derives through a set of chemical events involving *inter alia* the formation of humulene.[1] Besides being a favourite target of synthetic chemists,[2] an effect of its challenging angularly-fused triquinanic (*i.e.* cyclopenta-(c)-pentalenic) structure, **1** has also gained attention as an *in vivo* precursor of pentalenolactone, a related sesquiterpenoid displaying interesting antibiotic and antiviral properties.



octahydrocyclopenta-(c)-pentalene

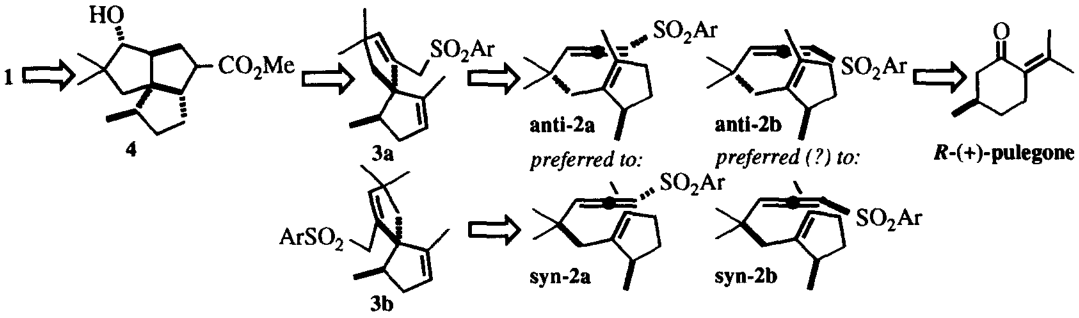


pentalenic acid, **1**



pentalenolactone

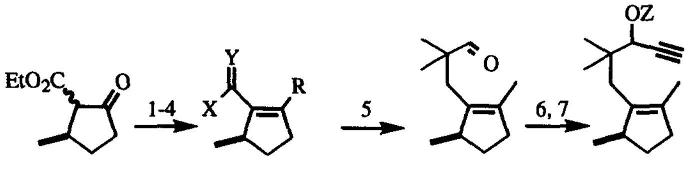
Given the ease with which certain allene sulfones could be isomerised into spiro sulfones by an intramolecular Alder-ene (IMAE) process,[3] we projected to synthesize **1** from pulegone via the allene sulfone **2** as shown.



It was anticipated that the IMAE reaction of sulfone **2** would be face-selective, occurring preferably through the "anti" conformation since the steric interactions between the allene moiety and the cyclopentene ring would then be minimal. As represented, this should be especially true for the diastereomer **2a**. In the event, the resulting allylic sulfone **3a** could conceivably suffer accurate function adjustments so as to give access to the triquinanic derivative **4**, indeed a precursor of the acid **1**.[2c] We describe in this letter how this planned synthesis was rendered effective.

The ketoester **5**, prepared from *R*-(+)-pulegone by sequential treatment with bromine, sodium ethoxide and ozone as described,[4a] was converted into the enol phosphate **6a**. Reacting **6a** with lithium dimethylcuprate in presence of TMSCl[4b] gave the ester **6b** (80%). DIBA-H reduction of **6b** afforded the alcohol **6c** which was treated by the (COCl)$_2$-DMF reagent[4c] to yield the chloride **6d** (48 % overall, from **5**).

Reagents and conditions: 1- *i*) NaH (1.3 eq.), ether; *ii*) (EtO)$_2$P(O)Cl (1.05 eq.), ether; 0°C, 30 min.; 2- Me$_2$CuLi (3 eq.), TMSCl (2 eq.); ether; -40 to -20°C, 4 hours; 3- DIBA-H (3 eq.), hexane; -78°C, 3 hours; 4- (COCl)$_2$ (4 eq.), DMF; 0°C, 2.5 hours; 5- (CH$_3$)$_2$CH=CHOTMS (1.4 eq.), ZnCl$_2$ (0.1 eq.), CH$_2$Cl$_2$; -50°C to 0°C, 4 hours; 6- C$_2$HLi, THF; -78°C to -20°C, 1 hour; 7- *p*-toluenesulfinyl chloride (1.25 eq.), NEt$_3$ (1.5 eq.), CH$_2$Cl$_2$; -78°C to r.t., 3 hours.



5

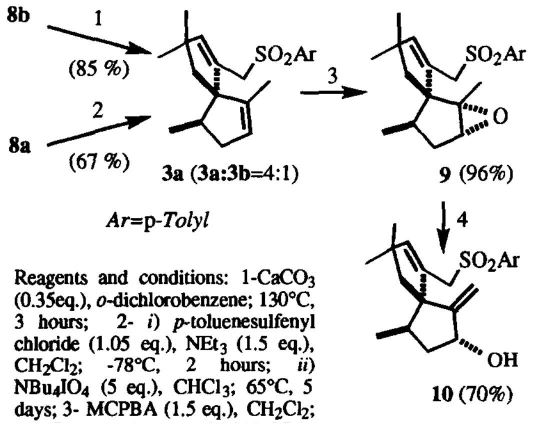
6a, R=OP(O)OEt$_2$; X=OEt; Y=O
6b, R=CH$_3$; X=OEt; Y=O
6c, R=CH$_3$; X=OH; Y=H,H
6d, R=CH$_3$; X=Cl; Y=H,H

7

8a, Z=H
8b, Z=S(O)-*p*-tolyl

The aldehyde **7** was obtained in fair yield (70%) by treatment of **6d** with the trimethylsilyl enol ether of *i*-butyraldehyde in CH$_2$Cl$_2$, in presence of ZnCl$_2$. Condensation of **7** with lithium acetylide gave the acetylenic alcohol **8a** which was transformed into the sulfinate **8b** (73%; from **7**) by treatment with *p*-toluenesulfinyl chloride.

Either heating a 0.4M solution of **8b** in *o*-dichlorobenzene for three hours or treating the alcohol **8a** by *p*-toluenesulfenyl chloride and oxidizing the transient allene sulfoxide by NBu$_4$IO$_4$ in refluxing CHCl$_3$ afforded the same 4/1 mixture of isomeric (NMR, elemental analysis), separable (column chromatography) sulfones.[5] Thorough NMR investigations (COSY, NOESY) allowed us to attribute the structure **3a** to the major component, the minor one being **3b**. Unequivocal confirmation of that assignment was brought forth by treating **3a** with MCPBA. The resulting epoxide -*i.e.* **9**- was heated in toluene with aluminium isopropoxide in excess to afford slowly, but cleanly, the allylic alcohol **10** (70%), which furnished a crystal suitable for X-ray analysis by recrystallisation from ether.[6]



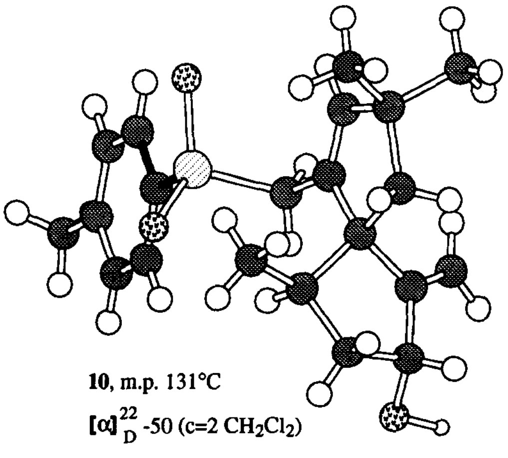
3a (**3a**:**3b**=4:1)

Ar=p-Tolyl

9 (96%)

10 (70%)

Reagents and conditions: 1-CaCO$_3$ (0.35eq.), *o*-dichlorobenzene; 130°C, 3 hours; 2- *i*) *p*-toluenesulfenyl chloride (1.05 eq.), NEt$_3$ (1.5 eq.), CH$_2$Cl$_2$; -78°C, 2 hours; *ii*) NBu$_4$IO$_4$ (5 eq.), CHCl$_3$; 65°C, 5 days; 3- MCPBA (1.5 eq.), CH$_2$Cl$_2$; -78°C to r.t., 4 hours; 4- Al(i-OPr)$_3$ (1.2 eq.x7), toluene; 110°C, 5 days.



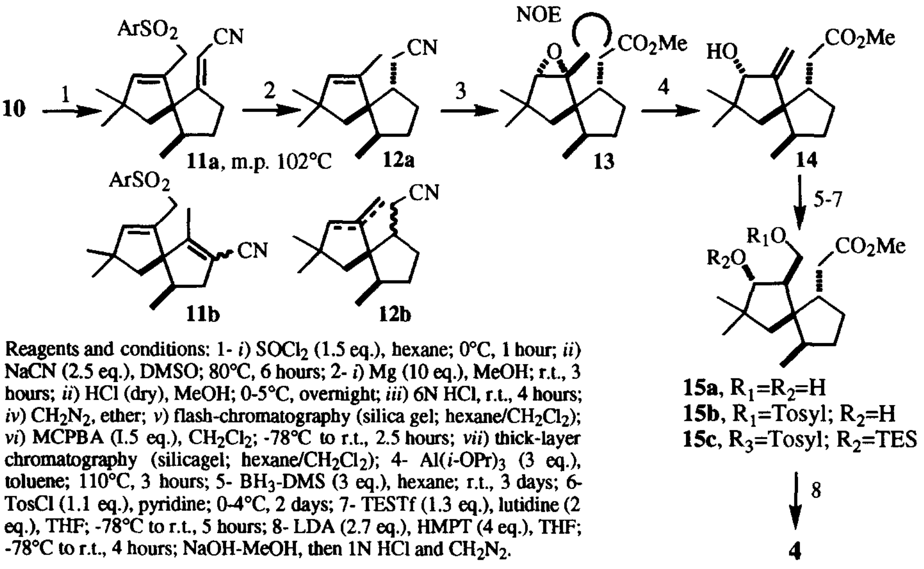
10, m.p. 131°C

$[\alpha]^{22}_{D}$ -50 (c=2 CH$_2$Cl$_2$)

The picture shown above, computer generated from crystal data,[7] clearly indicated that the ene reaction (leading to the allylic sulfone **3a**) had occurred effectively as predicted, with preferential attachment of the sp carbon atom to the cyclopentene ring at the opposite of the C1 (pentalenic acid numerotation)-methyl group. It is also worth noting the significant template effect displayed by the tosyl group in the epoxidation step.

The possibility to transform the sulfone **10** into a triquinanic compound was then briefly examined.

The sulfone **10** was treated successively by $SOCl_2$ in hexane and KCN in DMSO to afford a mixture of isomeric nitriles **11** (**11a**/**11b**=7/3) from which pure **11a** (64%) could be isolated by crystallisation (CH_2Cl_2/hexane). Both hydrogenolysis of the tosyl group and hydrogenation of the carbon carbon double bond bearing the cyano group were ensured by treatment of **11a** with Mg (excess) in methanol.[8] We expected that protonation of the carbanionic species, which would theoretically form during the reduction of the acrylonitrile moiety, would occur on the less hindered face hence leading to nitrile **12a**, which was effectively the major product. Isomers resulting either from protonation on the other side and/or from scrambling of the carbon carbon double bond of the allylic sulfone moiety during hydrogenolysis of the tosyl group were also produced however. Though **12a** could be purified at this stage by chromatography, it proved later advantageous to delay the separation operations. Hence, treatment of the nitrile **12** mixture by dry HCl in MeOH, then 6N HCl, gave the corresponding acids which were esterified (CH_2N_2). The major constituent (35%) was partially purified by flash-chromatography and treated by MCPBA. Careful chromatography on a thick layer of silica gel of the crude epoxidation product allowed the isolation of the epoxide **13** (12% overall yield, from **11a**) in pure state, its structure being established unambiguously by NMR. Of distinctive significance was the observation of the indicated NOE.



Reagents and conditions: 1- *i*) $SOCl_2$ (1.5 eq.), hexane; 0°C, 1 hour; *ii*) NaCN (2.5 eq.), DMSO; 80°C, 6 hours; 2- *i*) Mg (10 eq.), MeOH; r.t., 3 hours; *ii*) HCl (dry), MeOH; 0-5°C, overnight; *iii*) 6N HCl, r.t., 4 hours; *iv*) CH_2N_2, ether; *v*) flash-chromatography (silica gel; hexane/CH_2Cl_2); *vi*) MCPBA (1.5 eq.), CH_2Cl_2; -78°C to r.t., 2.5 hours; *vii*) thick-layer chromatography (silicagel; hexane/CH_2Cl_2); 4- Al(*i*-OPr)$_3$ (3 eq.), toluene; 110°C, 3 hours; 5- BH_3-DMS (3 eq.), hexane; r.t., 3 days; 6- TosCl (1.1 eq.), pyridine; 0-4°C, 2 days; 7- TESTf (1.3 eq.), lutidine (2 eq.), THF; -78°C to r.t., 5 hours; 8- LDA (2.7 eq.), HMPT (4 eq.), THF; -78°C to r.t., 4 hours; NaOH-MeOH, then 1N HCl and CH_2N_2.

Treatment of the epoxide **13** by aluminium isopropoxide proceeded smoothly, affording the allylic alcohol **14** which was hydroborated (BH_3-DMS). The selectivity of that step was rather low. Attempted improvement by operating in presence of Wilkinson's catalyst was ineffective.[9] The diol **15a** (28%) could be isolated by thick-layer chromatography anyway and subsequently transformed into the tosylate **15b** by treatment with tosyl chloride. Protection of the secondary hydroxy group as a O-TES derivative with triethylsilyl triflate then afforded **15c**. Adding an excess of LDA to a solution of compound **15c** in THF/HMPT led to the formation of an ester (34%; from **15a**) displaying NMR attributes fitting well the published data for the compound **4**.[2c,10]

In conclusion, the potential of the IMAE reaction of allene sulfones in synthesis of spiro compounds has been substantiated by preparing, from (*R*)-pulegone, a triquinanic compound. Further applications of these reactions are actively studied.

Acknowledgements: Best thanks are due to the Fondation Roussel-Uclaf for a grant (to C. B.-G.).

References and Notes

1- Seto, H; Sasaki, T.; Uzawa, J.; Takeuchi, S., Yonehara, H. *Tetrahedron Lett.* **1978**, *19*, 4411-4412.

2- a) Sakai, K.; Ohtsuka, T.; Misumi, S.; Shirahama, H.; Matsumoto, T. *Chemistry Letters* **1981**, 355-358; b) Crimmins, M.T.; DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800-806; c) Ihara, M.; Katogi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin I* **1988**, 2963-2970; d) Hudlicky, T.; Sinai-Zingde G.; Natchus, M. G.; Ranu, B. C.; Papadopoulos, P. *Tetrahedron* **1987**, *43*, 5685-5721; e) Agnel, G.; Negishi, E.-I. *J. Am. Chem. Soc.* **1991**, *113*, 7424-7426; f) Rowley, E. G.; Schore, N. E. *J. Org. Chem.* **1992**, *57*, 6853-6861; g) Wu, J.-Y.; Zhu, Y.-Y.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 104-110.

3- Bintz, C.; Uguen, D preceding letter in this issue. The results presented herein are taken in parts from the thesis dissertation of C. Bintz (University Louis Pasteur, Strasbourg, 1996).

4- a) Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602-1606; b) Sum, F.- W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431-1441. The use of TMSCl, supposed to trap the ethoxide ion which formed theoretically during the substitution process, proved to be essential for obtaining **6b** in high yield; c) Kocienski, P.; Todd, M. *J. Chem. Soc. Perkin I* **1983**, 1783-1787.

5- As observed precedently with related substrates (see ref. 3), the allene sulfone **2** which formed during the TBA periodate oxidation step rearranges at a remarkably low temperature. Obviously, the allene sulfone thus formed was a mixture of two diastereomers, which could be detected *exclusively* by splitting of a few signals in the ^{13}C NMR spectra.

6- Selected data: *i)* **3a**: m.p. 118°C; elemental analysis: C 73.25 (calc. 73.21), H 8.24 (calc. 8.19); ^{1}H NMR: 0.76 (d, J=6.8Hz, 3H), 1.02 (s, 3H), 1.06 (s, 3H),1.13-1.29 (m, 1H), 1.33 (d, J=1.6Hz, 3H), 1.56-2 (m, 3H), 2.17-2.29 (m, 1H), 2.44 (s, 3H), 3.59 (AB system, J_{AB}=15Hz, Δv=25Hz, 2H), 5.3 (s, 1H), 5.79 (s, 1H); 7.32 (d, J=8.3Hz, 2H), 7.75 (d, J=8.3Hz, 2H); $[\alpha]_D^{21}$ -80 (c=2, CH_2Cl_2); *ii)* **10**: m.p. 131°C; elemental analysis: C 70.06 (calc. 69.96), H 7.79 (calc. 7.83); ^{1}H NMR: 0.72 (d, J=6.7Hz, 3H), 1.03 (s, 3H), 1.05 (s, 3H), 1.23-1.45 (m, 2H), 1.7-1.9 (m, 2H), 2.03-2.21 (m, 1H), 2.44 (s, 3H), 3.64 (AB system, J_{AB}=15Hz, Δv=23Hz, 2H), 4.45 (d, J=6Hz, 1H), 4.6 (d, J=1.3Hz, 1H), 5.07 (d, J=1Hz, 1H), 5.98 (s, 1H), 7.32 (d, J=8.3Hz, 2H), 7.76 (d, J=8.3Hz, 2H); $[\alpha]_D^{21}$ -50 (c=2, CH_2Cl_2); *iii)* **13**: 0.94 (d, J=6.7Hz, 3H), 1.07 (s, 3H), 1.08 (s, 3H), 1-1.3 (m, 5H), 1.32 (s, 3H), 1.6-1.95 (m, 3H), 2.09, J=15.9, 9.5Hz, 1H), 2.4-2.6 (m, 1H), 2.77 (s, 1H), 2.98 (dd, J=15.8, 4.6Hz, 1H), 3.66 (s, 3H); ^{13}C NMR: 14.2, 13.6, 25.6, 26.6, 28.7, 30.2, 36.3, 37.3, 38.2, 40.5, 41.8, 51.4, 56. 70.3, 71.7, 174.3; *iv)* **15b**: 0.86 (d, J=6.4Hz, 3H), 0.92 (s, 3H), 1.03 (s, 3H), 1.4-2.5 (m, 11H), 2.45 (s, 3H), 3.5-4 (m, 3H), 3.63 (s, 3H), 7.35 (d, J=8Hz, 2H), 7.81 (d, J=8Hz, 2H). All the ^{1}H and ^{13}C NMR spectra which are described herein were recorded at 200MHz and 50MHz, respectively, in $CDCl_3$.

7- Crystal data for **10** ($C_{21}H_{28}O_3S$; M=360.5): orthorhombic, space group $P2_12_12_1$, a=9.522(2), b=13.747(4), c=30.859(9) Å, U=4039.5 $Å^3$, z=8, dcalc=1.186 gcm^{-3}, μ(MoKα)=1.674 cm^{-1}, λ=0.7107 Å. Intensities of 4627 independent reflections with θ in the range 2/26° were measured on a Enraf-Nonius CAD4-F diffractometer at 20°C, $\theta/2\theta$ scan mode, dimensions of the colorless crystal 0.40x0.40x0.30 mm^3. The structure was solved by direct methods and refined by full-matrix least squares first (F) with isotropic and then with anisotropic thermal parameters for all non hydrogen atoms using 2784 observed reflections with $I>3\sigma(I)$. Empirical absorption corrections from psi scans of 4 reflections (abs min and max=0.97/1.00). The hydrogen atoms were located in difference Fourier maps and included in structure factor calculation but not refined. The absolute structure was determined by comparing x,y,z and -x,-y,-z refinements and confirmed by calculating Flack's x parameter. Final R(F) and Rw(F) values are 0.037 and 0.053, GOF=1.077 for p+0.08 in $\sigma^2(Fo)=\sigma^2_{count} + (pI)^2$. A CIF has been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (U.K.). They may be obtained on request from the Director by citing the full reference to this communication.

8- Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127-128.

9- Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **1988**, *110*, 6917-6918.

10- Due to the very low amount of material thus isolated, the purity of the sample was incomplete. However, the ^{1}H NMR spectra of that ester displayed basically signals attributable to the ester **4** (see ref. 2c): 0.89 (d, J=6.2 Hz, 3H), 0.93 (s, 3H), 1.04 (s, 3H), 1.15-2.8 (2m, 13H (plus O*H*), 3.41 (d, J=7.5Hz, 1H), 3.66 (s, 3H).

(*Received in France* 2 *February* 1997; *accepted* 5 *March* 1997)