Tetrahedron Letters, Vol. 34, No. 30, pp. 4789-4792, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

# Acid-Mediated Cyclisations: Efficient Access to Functionalised *trans*-Decalins

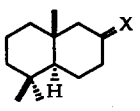
**Simon M. Linder, Daniel Reichlin, Dana P. Simmons[1] and Roger L. Snowden***

*Firmenich SA*, Research Laboratories, P.O. Box 239, CH-1211 Geneva 8, Switzerland.

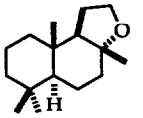
*Key Words:* cyclisation; decalin; β-oxyenoate; acid-mediation; polyene

***Abstract:*** Acid-mediated cyclisation of monocyclic, (*E*)- and (*Z*)-β-phosphoroxyenoate **5d** using 98% aq. $H_2SO_4$ in toluene at 2° affords, after decarbomethoxylation, *trans*-2-decalone **1** in 79% and 68% yield, respectively.

C(2)-oxygen functionalised *trans*-5,5,9-trimethyldecalins **1** and **2**[2], and the structurally related tricyclic ether **3**[3] represent organoleptically active compounds which are highly appreciated in perfumery. The most direct access to these compounds is *via* acid-mediated cyclisation of suitably functionalised acyclic or monocyclic



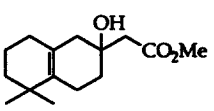
**1** X = O
**2** X = H, β-OAc



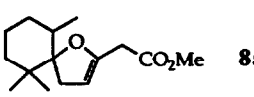
**3**

polyene precursors[2,4], whose stereochemical course is determined by whether or not the cyclisation process is slow or rapid compared with conformational equilibration of carbocationic intermediates[5]. Stereoselective access to a direct precursor of **1**, β-keto ester **6a**, by treatment of either acyclic or monocyclic β-keto esters, **4** or **5**, with $SnCl_4$ in $CH_2Cl_2$, has also been described[6], the reactions presumably proceeding by proton mediated cyclisation of *in situ* formed (*Z*)-β-stannyloxyenoates **4a** and **5a**. More recently[7], a variant of this process has been reported, involving the $BF_3{\cdot}MeNO_2$ mediated cyclisation of (*Z*)- and (*E*)-β-silyloxyenoates **4b** to **6a** and **6b**, respectively. This latter report prompts us to present herein a closely related study whose principal goal was the development of an efficient route from **5** to **1** which avoids the use of stoichiometric quantities of a *Lewis* acid.

A preliminary experiment verified that treatment of **5** with 98% aq. $H_2SO_4$ (2 mol-equiv.) in toluene at 2° afforded neither **6a** nor **6b**, but gave instead a complex mixture from which the two major products, **7** (27% yield) and **8a,b** (2:1 diastereoisomeric mixture, 25% yield)[8], both originating from participation of the ketone group, were isolated. We thus reasoned that protection of the β -keto ester moiety of **5** as a β-oxyenoate, prior to cyclisation, might provide a practical solution to this problem. Consequently, we first investigated the



**7**



**8a,b**

acid-mediated cyclisation of β-silyloxyenoate **5b** (*E*/*Z*<1:20) and β-acetoxyenoate **5c** (*E*/*Z* 1:5), both readily prepared from **5**, in *ca.* 75% yield, using protic conditions (*viz.* RCl (1.2 mol-equiv.), $Et_3N$ (1.2 mol-equiv.), toluene r.t.). After treatment with 98% aq. $H_2SO_4$ in toluene, the crude mixtures were directly submitted to

decarbomethoxylation conditions (*viz.* KOH, EtOH-$H_2O$ then aq. HCl) in order to convert to **1** any **6a,b** formed in the first step. The results were disappointing (*cf. entries 1, 2: Table*). Not only was the yield of **1** poor, 14% and 32% respectively, but GC analysis indicated that hydrolysis of **5b** and **5c** to **5** is competitive with the desired cyclisation process.

***Table.*** *Two-step transformation of* **5b-d** *to* **1**[a)]

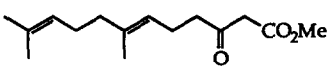
| Entry | Substrate | *E/Z* [b)] | **1** (Yield%)[c)] | Selectivity[d)] |
|---|---|---|---|---|
| 1 | **5b** | <1:20 | 14 | 27:1 |
| 2 | **5c** | 1:5 | 32 | 7:1 |
| 3 | **5d** | >20:1 | 79 | 38:1 |
| 4 | **5d** | <1:20 | 68 | 19:1 |

a) **cyclisation:** substrate (1 g), 98% aq. $H_2SO_4$ (2 mol-equiv.), toluene, 2°, followed by extractive workup (toluene). **decarbomethoxylation:** KOH (1.7 mol-equiv.), EtOH-$H_2O$ 1:1, reflux, 45 min, then aq. HCl (excess), extractive workup ($Et_2O$) and *Kugelrohr* distillation.

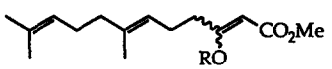
b) *E/Z*-ratios estimated by GC and NMR analysis; in particular, in their $^1$H-NMR spectra, the (*E*)- and (*Z*)-isomers are distinguished by the characteristic higher chemical shift of H-C(2) in the former isomer[8].

c) Yield determined by GC analysis of distilled product; identification of products effected by comparison with authentic samples[1].

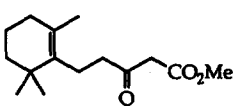
d) Selectivity refers to the ratio of **1** to its *cis*-fused decalin epimer.



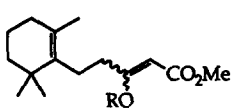

**4**



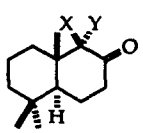

**4a** R = $SnCl_3$
**4b** R = Si(*t*Bu)$Me_2$




**5**




**5a** R = $SnCl_3$
**5b** R = Si(*t*Bu)$Me_2$
**5c** R = C(O)Me
**5d** R = P(O)$(OEt)_2$




**6a** X = $CO_2$Me, Y = H
**6b** X = H, Y = $CO_2$Me

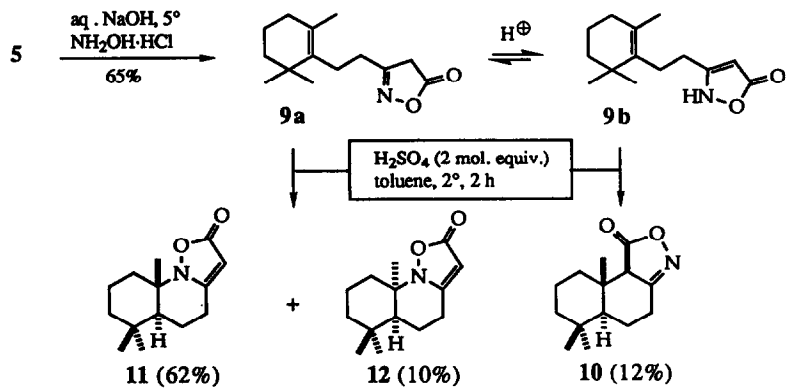
Realising that a more hydrolytically stable β-oxyenoate was required, we selected β-diethoxyphosphoroxyenoate **5d** as a cyclisation substrate. Accordingly, both (*E*)-and (*Z*)-**5d** were stereoselectively prepared from **5**, using respectively protic conditions (*i.e.* as for **5b,c** plus the catalytic presence of DMAP (0.03 mol-equiv.)[9]: 80% yield) and aprotic conditions (*viz.* $(EtO)_2P(O)Cl$ (1.2 mol-equiv.), NaH (1 mol-equiv.), THF r.t.[9]: 84% yield). Gratifyingly, submission of these two substrates to the foregoing cyclisation/decarbomethoxylation procedure afforded **1** in satisfactory yields of 79% and 68%, respectively (*cf. entries 3, 4*)[10].

For all four cyclisations the remarkably high *trans*-selectivity with respect to the ring junction stereochemistry is striking, the ratio of **1** to its *cis*-fused decalin epimer varying from 7:1 to 38:1 (*cf. Table*).

Mechanistically, this result indicates that the major reaction pathway involves a non-concerted process, in which C-C bond formation is slow compared to conformational equilibration[5].

Finally, the acid-mediated cyclisation of another derivative of **5** was examined (*cf. Scheme*). It was hoped that isoxazolone **9a** (m.p. 57-58°) would cyclise, *via* tautomer **9b**, to isoxazolone **10**, which could provide access

*Scheme*




to **1** after N-O hydrogenolysis and decarboxylative hydrolysis[11]. In fact, cyclisation of **9a** afforded **10** (m.p. 111-113°) in only 12% yield; the major product being isoxazolone **11** (m.p. 102-103°: 62% yield) accompanied by its *cis*-fused epimer **12** (m.p. 108-109°; 10% yield)[12]. This unexpected preference for ring closure *via* formation of a C-N bond is of synthetic interest, as access to nitrogen heterocycles *via* acid-mediated cyclisation is generally precluded by preferential protonation of the amino group[5]. It is also noteworthy that C-N bond formation is less stereoselective than C-C bond formation with respect to the ring junction stereochemistry, a result which indicates a lower energy difference between the respective transition states leading to **11** and **12**.

## REFERENCES AND NOTES


1. Present address: *Ciba-Geigy*, Agricultural Division, P.O. Box 18300, Greensboro NC 27419-8300, USA.
2. Ohloff, G.; Näf, F.; Decorzant, R.; Thommen, W.; Sundt, E. *Helv. Chim. Acta* **1973**, *56*, 1414-1448.
3. *Ambrox®* ((–)-**3**, trade name of *Firmenich SA*) is a commercially important odorant naturally occurring in ambergris, see: Ohloff, G. in *Fragrance Chemistry*, ed. Theimer, E.T., Academic Press, New York, **1982**, pp. 535-573.
4. Snowden, R.L.; Eichenberger, J.-C.; Linder, S.M.; Sonnay, P.; Vial, C.; Schulte-Elte, K.H. *J. Org. Chem.* **1992**, *57*, 955-960.
5. Bartlett, P.A. in *Asymmetric Synthesis*, ed. Morrison, J.D., Academic Press, New York, **1982**; Vol. 3, Part B; pp. 341-454.
6. White, J.D.; Skeean, R.W.; Trammell, G.L. *J. Org. Chem.* **1985**, *50*, 1939-1948; Büchi, G.; Wüest, H. *Helv. Chim. Acta* **1989**, *72*, 996-1000.
7. Harring, S.R.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.* **1992**, 503-505.
8. All chiral compounds described in this work are racemic; analytical data of **5b-d**, **7-12**: (*E*)-**5b**: $^1$H-NMR (H-C(2)): 5.13. (*Z*)-**5b**: $^1$H-NMR (H-C(2)): 5.04. $^{13}$C-NMR: 98.0 (C(2)), 34.2 (C(4)). (*E*)-**5c**: $^1$H-NMR (H-C(2)): 5.67. (*Z*)-**5c**: $^1$H-NMR (H-C(2)): 5.63. $^{13}$C-NMR: 106.4 (C(2)), 36.0 (C(4)). (*E*)-**5d**: $^1$H-NMR (H-C(2)): 5.86. $^{13}$C-NMR: 104.6 (C(2)), 32.6 (C(4)). (*Z*)-**5d**: $^1$H-NMR (H-C(2)): 5.41. $^{13}$C-NMR: 104.5 (C(2)), 35.7 (C(4)).

**7**: $^1$H-NMR: 0.98 (*s*, 3H); 1.00 (*s*, 3H); 1.45 (*m*, 2H); 1.50-2.10 (9H); 2.21 (*m*, 1H); 2.50 (2H); 3.73 (*s*, 3H). $^{13}$C-NMR: 173.2 (*s*), 134.0 (*s*), 124.6 (*s*), 69.2 (*s*), 51.6 (*q*), 43.7 (*t*), 43.5 (*t*), 39.6 (*t*), 34.3 (*t*), 33.6 (*s*), 31.3 (*t*), 27.9 (*q*), 27.8 (*q*), 22.0 (*t*), 19.3 (*t*). MS: 252 (0, $M^{+\cdot}$), 234 (12), 219 (39), 145 (94), 121 (33), 105 (34), 91 (51), 74 (100).

**8a**: $^1$H-NMR: 0.80 (*d*, *J* = 7, 3H); 0.80 (*s*, 3H); 0.95 (*s*, 3H); 1.20-2.25 (9H); 2.95-3.30 (2H); 3.65 (*s*, 3H); 5.25 (*m*, 1H). $^{13}$C-NMR: 179.0 (*s*), 169.7 (*s*), 96.8 (*s*), 86.7 (*d*), 50.4 (*q*), 39.2 (*s*), 36.8 (*d*), 36.5 (*t*), 32.4 (*t*), 30.9 (*t*), 27.1 (*t*), 24.7 (*q*), 23.1 (*q*), 15.7 (*q*). MS: 252 (8, $M^{+\cdot}$), 181 (17), 137 (22), 123 (54), 82 (100).

**8b**: $^1$H-NMR: 0.76 (*d*, *J* = 7, 3H); 0.82 (*s*, 3H); 1.07 (*s*, 3H); 1.20-2.25 (9H); 2.95-3.30 (2H); 3.65 (*s*, 3H); 5.24 (*m*, 1H). $^{13}$C-NMR: 178.4 (*s*), 169.6 (*s*), 98.0 (*s*), 86.7 (*d*), 50.4 (*q*), 39.2 (*s*), 38.3 (*t*), 35.3 (*d*), 32.6 (*t*), 32.4 (*t*), 25.0 (*q*), 22.6 (*t*), 21.3 (*q*), 21.1 (*t*), 15.0 (*q*). MS: 252 (8, $M^{+\cdot}$), 181 (15), 137 (50), 123 (76), 82 (100).

**9a**: $^1$H-NMR: 1.01 (*s*, 6H); 1.44 (*m*, 2H); 1.58 (*m*, 2H); 1.62 (*s*, 3H); 1.93 (*t*, *J* = 7, 2H); 2.32 (4H); 3.42 (*s*, 2H). $^{13}$C-NMR: 175.2 (*s*), 166.8 (*s*), 135.3 (*s*), 129.3 (*s*), 39.7 (*t*), 35.9 (*t*), 35.0 (*s*), 32.8 (*t*), 29.9 (*t*), 28.5 (2*q*), 24.7 (*t*), 19.9 (*q*), 19.4 (*t*). MS: 235 (1, $M^{+\cdot}$), 220 (5), 176 (24), 162 (45), 121 (100), 93 (60), 81 (60).

**10**: IR: 1778. $^1$H-NMR: 0.88 (*s*, 3H); 0.94 (*s*, 3H); 0.98 (*s*, 3H); 1.20-1.65 (7H); 2.03 (*m*, 1H); 2.29 (*m*, 1H); 2.36 (*m*, 1H); 2.80 (*m*, 1H); 2.84 (*s*, 1H). $^{13}$C-NMR: 176.4 (*s*), 167.7 (*s*), 57.7 (*d*), 52.7 (*d*), 41.9 (*t*), 41.6 (*s*), 38.5 (*t*), 33.7 (*q*), 33.7 (s), 26.6 (*t*), 22.3 (*t*), 21.7 (*q*), 18.3 (*t*), 15.0 (*q*). MS: 235 (7, $M^{+\cdot}$), 220 (17), 164 (22), 152 (24), 138 (22), 69 (100).

**11**: IR: 1720. $^1$H-NMR: 0.87 (*s*, 3H); 1.00 (*s*, 3H); 1.09 (*s*, 3H); 1.31 (*m*, 1H); 1.40-1.80 (6H); 1.88 (*m*, 1H); 2.23 (*m*, 1H); 2.59 (*m*, 1H); 2.82 (*m*, 1H); 5.00 (*d*, *J* = 1.5, 1H). $^{13}$C-NMR: 171.9 (*s*), 166.3 (*s*), 89.5 (*d*), 66.1 (*s*), 50.7 (*d*), 41.0 (*t*), 37.0 (*t*), 33.3 (*s*), 32.9 (*q*), 24.4 (*t*), 21.1 (*q*), 18.5 (*t*), 18.0 (*t*), 15.5 (*q*). MS: 235 (51, $M^{+\cdot}$), 220 (69), 192 (36), 164 (53), 152 (54), 138 (69), 69 (100).

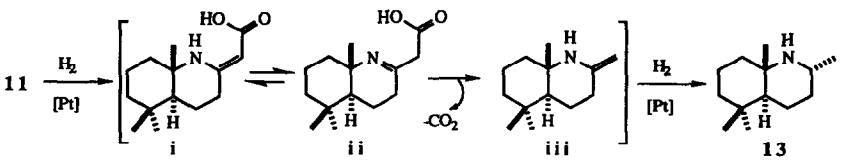
**12**: IR: 1724. $^1$H-NMR: 1.04 (*s*, 3H); 1.11 (*s*, 3H); 1.17 (*s*, 3H); 1.24-1.40 (2H); 1.47 (2H); 1.58 (*m*, 1H); 1.73 (*m*, 1H); 2.02 (2H); 2.44 (br. *d*, *J* = 14.5, 1H); 2.73 (*m*, 1H); 2.89 (*m*, 1H); 5.02 (*s*, 1H). $^{13}$C-NMR: 171.6 (*s*), 167.4 (*s*), 89.2 (*d*), 64.8 (*s*), 49.9 (*d*), 42.2 (*t*), 35.7 (*t*), 34.6 (*s*), 32.5 (*q*), 25.0 (*q*), 24.7 (*q*), 23.0 (*t*), 18.1 (*t*), 17.4 (*t*). MS: 235 (27, $M^{+\cdot}$), 220 (100), 192 (20), 164 (38), 152 (28), 138 (39), 69 (52).


9. Asao, K.; Iio, H.; Tokoroyama, T. *Synthesis* **1990**, 382-386.

10. In contrast to the stereospecific *Lewis* acid mediated cyclisations of (*E*)- and (*Z*)-**4b**[7], the cyclisations of (*E*)- and (*Z*)-**5d** afford 1.9:1 and 2.8:1 **6a,b** mixtures respectively. This is almost certainly due to epimerisation of **6a,b**; indeed, independent treatment of **6a** and **6b** with 98% aq. $H_2SO_4$ in toluene established that a 1.9:1 **6a,b** mixture corresponds to thermodynamic equilibrium.

11. Shaw, G. *J. Chem. Soc.* **1950**, 720-723.

12. Structural confirmation of **11** was obtained by catalytic hydrogenation ([$PtO_2$], AcOH-AcOEt 3:1, 20°) to perhydroquinoline **13** (17% yield). This multistep transformation is believed to proceed *via* intermediates **i-iii** in a reaction sequence involving hydrogenolysis of the N-O bond, tautomerism, decarboxylation, and stereoselective hydrogenation from the β-face.


*Data of* **13**: $^1$H-NMR: 0.77 (*s*, 3H); 0.81 (*s*, 3H); 1.00 (*d*, *J* = 7, 3H); 0.95-1.70 (11H); 1.16 (*s*, 3H); 1.79 (*m*, 1H); 2.95 (*m*, 1H). $^{13}$C-NMR: 54.6 (*d*), 53.4 (*s*), 45.6 (*d*), 42.3 (*t*), 42.2 (*t*), 37.0 (*t*), 33.1 (*s*), 32.6 (*q*), 23.4 (*q*), 20.9 (*q*), 20.8 (*q*), 20.6 (*q*), 19.7 (*t*). MS: 195 (7, $M^{+\cdot}$), 180 (100), 152 (58), 124 (13), 110 (15), 96 (14).

(Received in France 22 April 1993; accepted 4 June 1993)