Tetrahedron Vol. 36, pp. 393–396
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0040-4020/80/0201-0393/$02.00/0

# A ONE STEP SYNTHESIS OF 2,4-DIALKOXYBICYCLO[3.2.1]OCTAN-8-ONES

## STEREOCHEMICAL ASSIGNMENTS USING THE LANTHANIDE NMR SHIFT REAGENT, Eu(FOD)$_3$

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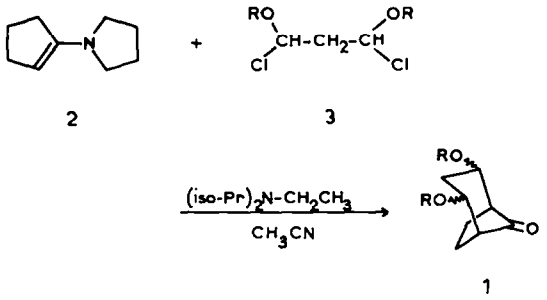
(*Received in UK* 10 *May* 1979)

**Abstract**—Several 2,4-dialkoxybicyclo[3.2.1]octan-8-ones have been prepared as mixtures of stereoisomers which could be separated and characterised by 60 MHz $^1$H NMR spectroscopy using Eu(FOD)$_3$.

We have synthesised, as synthons equivalent to a 2-oxocyclopentane-1,3-dicarboxylic acid,[1] a series of 2,4-dialkoxybicyclo[3.2.1]octan-8-ones, **1**, by condensation of N-(1-cyclopentenyl)pyrrolidine, **2**, with the corresponding 1,3-dialkoxy-1,3-dichloropropanes, **3**,[2] in the presence of 1,5 equiv. of diisopropylethylamine in acetonitrile as solvent[3] (Scheme 1).



2 3 1

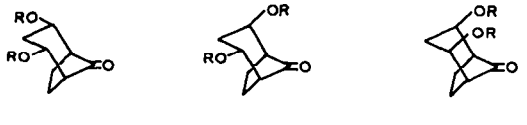
1a, 3a, R=Me 1b, 3b, R=Et
1c, 3c, R=isoPr 1d, 3d, R=PhCH$_2$–

Scheme 1.

The reaction yields a mixture of stereoisomers, **4**, **5**, and **6**, and we have studied the influence of the alkyl group R in the ratio which they are formed, Fig. 1.

Total yields and stereoisomer ratios for these reactions are given in Table 1.

We have isolated compounds **4a**, **5a**, **4b**, **5b**, **5c**, **6c** and **5d** by column chromatography



4 5 6

4a, 5a, R=Me 4b, 5b, R=Et
5c, 6c, R=isoPr 5d, R=PhCH$_2$–

Fig. 1.

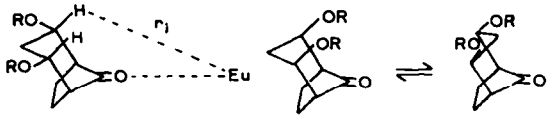
Table 1. Total yields and stereoisomer ratios for the synthesis of 2,4-dialkoxybicyclo[3.2.1]octan-8-ones.

| | | ratio[b] | | |
|---|---|---|---|---|
| | 1[a] | 4 | 5 | 6 |
| a | 39.8 | 13 | 87 | |
| b | 47.7 | 36 | 64 | |
| c | 6.5 | | 79 | 21 |
| d | 2.6 | | 100 | |

[a] Yields refer to distilled products for **1a** and **1b**, and to distilled and chromatographed products for **1c** and **1d**.
[b] The ratios were obtained from the integrated chromatogrammes. Integration errors were less than 3%, as shown by chromatographic analysis of standard mixtures of **4a–5a** and **4b–5b**.

($SiO_2$/Hexane: ether). Stereochemistry has been assigned by 60 MHz $^1$H NMR spectroscopy using the lanthanide shift reagent, Europium tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctanedionate), Eu(FOD)$_3$.

Stereoisomers **5a**, **5b**, **5c** and **5d** are readily identified because their NMR spectrum, on addition of 0,3 equiv. of Eu(FOD)$_3$, give two different absorptions for the alkoxyl groups, while stereoisomers **4** or **6**, with a plane of symmetry will give only one type of signals for the enantiotopic alkoxyl groups. The conformation most favourable for stereoisomers **4**, must be that in which the cyclohexanone ring has a chair conformation with equatorial alkoxyl groups. However, for stereoisomers **6**, the conformation with a chair cyclohexanone ring would have axial alkoxyl



4 6chair 6boat

Fig. 2.

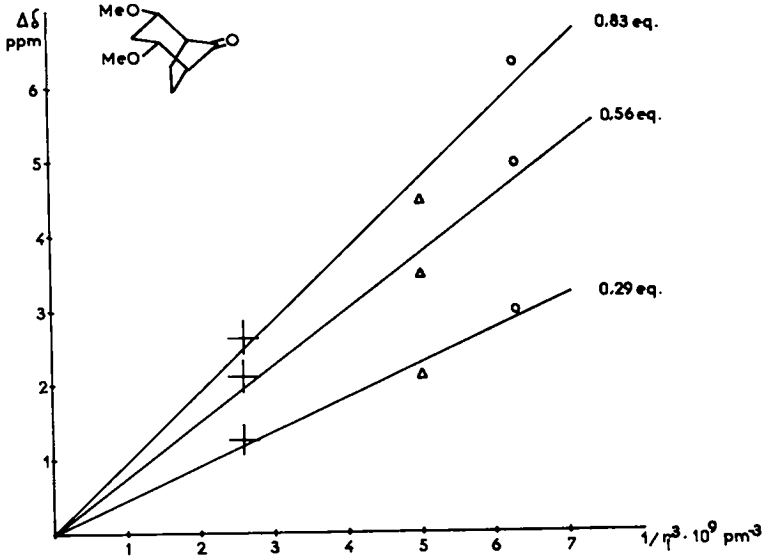



Fig. 3. LICS *vs* $1/r_i^3$ for the annular protons of **4a** or **6a**, ($H_1$ and $H_5$ (O), $H_2$ and $H_4$ (Δ), $H_3$, $H_6$ and $H_7$ (+)[a]), at 0,29, 0,56 and 0,83 Eu(FOD)$_3$/Substrate molar ratios, assuming configuration **4a**. (a) For these protons Δδ cannot be exactly determined. Maximum and minimum possible Δδ and $1/r_i^3 \cdot 10^9$ values for these protons are (+)±0,7 ppm and (+)±0,65 pm$^{-3}$ respectively.

groups, and therefore, a conformation with a boat cyclohexanone ring and equatorial alkoxyl groups might be important too (in this conformation there are not 1,4-diaxial hydrogen interactions), Fig. 2.

Assuming that the coordination of the Eu(FOD)$_3$ takes place at the carbonyl O atom and, in average, at 300 pm in the direction of the C—O bond,[4] the representation of the lanthanide induced chemical shifts, LICS, for the annular protons of the symmetric stereoisomers **4a** or **6a** and **4b** or **6b** at different Eu(FOD)$_3$/Substrate ratios *vs* $1/r_i^3$, being $r_i$ the distance in pm between the Europium atom and the proton under consideration, gives straight lines passing through the coordinates origin, Fig. 3 and 4, when it is considered that the symmetric stereoisomers are **4a** and **4b**, and no correlation, if it is considered that they are **6a** and **6b** with a chair of boat cyclohexanone ring.

However, for the symmetric stereoisomer **4c** or **6c**, no correlation is obtained, when it is considered that it is **4c**, or **6c** with a chair or boat cyclohexanone ring. In this case, a correlation is obtained assuming that it is **6c** and that the Europium atom coordinates both the carbonyl and the ether oxygen atoms and that in average it lies in the plane of symmetry of the molecule at 300 pm of the carbonyl oxygen atom with an angle C=O—Eu of 120°, Fig. 5.

The high proportion of the axial-equatorial stereoisomers, **5**, in all the cases studied may be

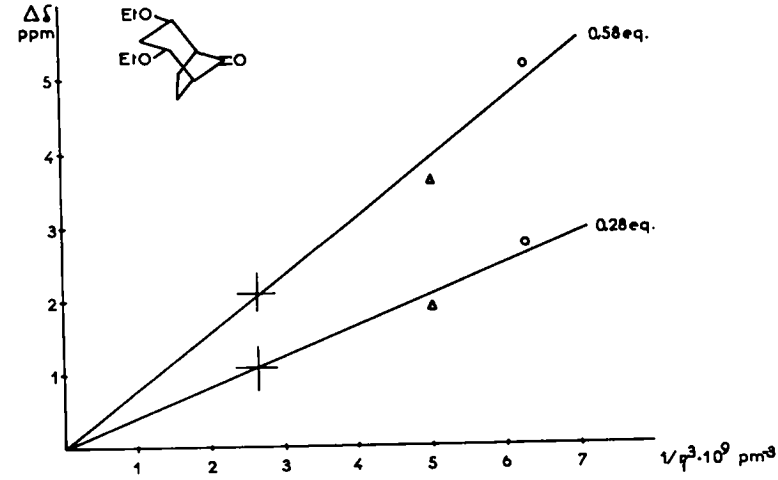



Fig. 4. LICS *vs* $1/r_i^3$ for the annular protons of **4b** or **6b**, ($H_1$ and $H_5$ (O), $H_2$ and $H_4$ (Δ), $H_3$, $H_6$ and $H_7$ (+)[a]), at 0,28 and 0,58 Eu(FOD)$_3$/Substrate molar ratios, assuming configuration **4b**. (a) For these protons Δδ cannot be exactly determined. Maximum and minimum possible Δδ and $1/r_i^3 \cdot 10^9$ values for these protons are (+)±0,7 ppm and (+)±0,65 pm$^{-3}$ respectively.

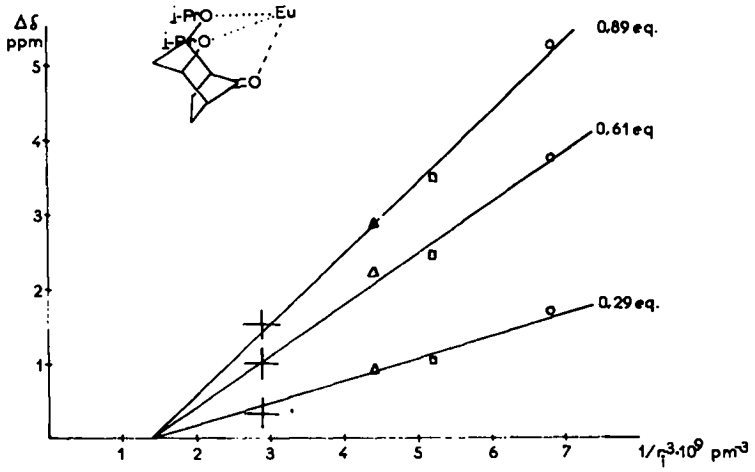



Fig. 5. LICS *vs* $1/r_i^3$ for the annular protons of **4c** or **6c**, ($H_1$ and $H_5$ (○), $H_2$ and $H_4$ (△), $H_{3\text{-exo}}$ (□), $H_{3\text{-endo}}$, $H_6$ and $H_7$ (+)[a]), at 0,29, 0,61 and 0,89 Eu(FOD)$_3$/Substrate molar ratios, assuming configuration **6c** and that the Europium atom coordinates both the carbonyl and the ether oxygen atoms. (a) For these protons Δδ cannot be exactly determined. Maximum and minimum possible Δδ and $1/r_i^3 \cdot 10^9$ values for these protons are (+) ± 0,6 ppm and (+) ± 0,3 pm$^{-3}$ respectively.

Table 2. Chemical shifts for the $C_2$ protons of *meso*- and *dl*-1,3-dialkoxy-1,3-dichloropropanes, and approximate ratios *meso*/*dl* deduced from the $^1$H NMR spectrum.

| | δ meso[b] | δ dl[b] | ratio meso/dl |
|---|---|---|---|
| 3a | 2.63 2.64 | 2.66 | 1/3 |
| 3b | 2.63 2.64 | 2.67 | 1/3 |
| 3c | 2.60 broad | 2.65 | 1/1 |
| 3d[a] | 2.67 | 2.70 | ? |

[a] **3d** cannot be distilled.

[b] Coupling constants are approximately 6 Hz in all cases.

partly explained if it is assumed an $S_N2$ mechanism for the two alkylation steps of this reaction, because the alkylating agents are mixtures of stereoisomers in the ratio indicated in Table 2.

The *meso* form of **3** will give the symmetric stereoisomers **4** or **6**, while the *dl* form of **3** will give the non symmetric stereoisomer **5**.

Moreover, the stereoisomers **4** seem to be oxidized by atmospheric oxygen more rapidly than the other stereoisomers. Thus, a mixture of **4b** and **5b** in the ratio 36/64, after one month exposed to the air was transformed into a mixture of **4b** and **5b** in the ratio 17/83, together with other products; and pure **4b**, freshly prepared, give an MS spectrum with the molecular ion at $M^+ = 212$, which disappears gradually on air exposure to give a new ion at $M^+ = 228$.

The distinction between *meso*- and *dl*-1,3-dialkoxy-1,3-dichloropropanes by $^1$H NMR spectroscopy might be effected because for the *meso*-form the protons at $C_2$ are diastereotopic and give two triplets of equal intensity whereas in the *dl*-form both protons are equivalent and give only one triplet, Fig. 6.

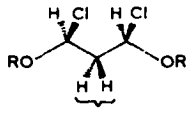
The chemical shifts for the protons at $C_2$ of *meso*- and *dl*-1,3-dialkoxy-1,3-dichloropropanes are given in Table 2.

## EXPERIMENTAL

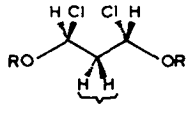
60 MHz $^1$H NMR spectra have been recorded on a Perkin Elmer R-12 spectrometer; MS spectra on a Hewlett Packard, mod. 5930 A spectrometer, and GLC on a Hewlett Packard mod. 5831 A chromatograph.

1,1,3,3,-*Tetraisopropoxypropane.* 11 g (67 mmole) of 1,1,3,3-tetramethoxypropane, 120 g (2 mole) of i-PrOH and a catalytic amount of *p*-TsOH were heated (bath at 115°) for 144 hr, the course of the reaction being controlled by $^1$H NMR spectroscopy. The mixture was distilled, first at atmospheric pressure and then at 10 torr, yield of 1,1,3,3-tetraisopropoxypropane 14,4 g, 78%, b.p. 107–117°/10 torr. NMR ($CCl_4$), δ 4,55 (t, J = 6 Hz, 2H), 3,80 (h, J = 6 Hz, 4H, 1,73 (t, J = 6 Hz, 2H), 1,13 and 1,10 (doublets, J = 6 Hz, 24H).

1,1,3,3-*Tetrabenzyloxypropane.* It was prepared as is described for 1,1,3,3-tetraisopropoxypropane, using only a little excess of benzyl alcohol, yield 80%, b.p. 245–250°/0.25 torr. NMR ($CCl_4$), δ 7,10 (s, 20H), 4,70 (t, J = 6 Hz, 2H), 4,37 and 4,40 (singlets, 8H), 2,05 (t, J = 6 Hz, 2H). (Found: C, 79,43%; H, 6,97. $C_{31}H_{32}O_4$ requires: C, 79,46%; H, 6,88%).




Diastereotopic protons




Equivalent protons

meso-1,3-Dialkoxy-1,3-dichloropropanes dl-1,3-Dialkoxy-1,3-dichloropropanes

Fig. 6.

1,3-*Diisopropoxy*-1,3-*dichloropropane*, **3c**.[2] Yield of distilled product 54%, b.p. 45°/0.1 torr.

*General procedure for the synthesis of* 2,4-*dialkoxybicyclo*[3.2.1]*octan*-8-*one*, **1**.[3] In a 250 ml 3-necked flask, fitted with mechanical stirring, reflux condenser, addition funnel and $N_2$ atmosphere, 76 mmole of **2**, and 114 mmole ethyldiisopropylamine in 90 ml acetonitrile were introduced and the flask was immersed in an ice bath while 76 mmole of **3**, were slowly added with vigorous stirring. The mixture was heated at 100° for 16 hr, then 120 ml water was added and the mixture stirred at room temp for 24 hr. The alkaline soln (NaOHaq) was extracted with ether (15 portions of 70 ml). The combined ether extracts were washed with water and dried with $Na_2SO_4$. Evaporation of the filtrate give the crude product which was distilled and in the case of **1c** and **1d**, was further chromatographed on silica gel using hexane/ether 1/1 as eluent.

2,4-*Dimethoxybicyclo*[3.2.1]*octan*-8-*one*, **1a**, yield 40% of distilled product, b.p. 136–140°/18 torr. (Found: C, 64,98%; H, 9,00. $C_{10}H_{16}O_3$ requires: C, 65,19%; H, 8,75%).

2,4-*Diethoxybicyclo*[3.2.1]*octan*-8-*one*, **1b**, yield 47% of distilled product, b.p. 96–100°/1 torr. (Found: C, 67,74%; H, 9,59. $C_{12}H_{20}O_3$ requires: C, 67,89%; H, 9,50%).

2,4-*Diisopropoxybicyclo*[3.2.1] *octan*-8-*one*, **1c**, yield of distilled and chromatographed product 6,5%, b.p. 120–130°/0.25 torr.

(1*RS*,2*RS*,4*RS*,5*SR*)-2,4-*Dibenzyloxybicyclo*[3.2.1]-*octan*-8-*one*, **5d**, yield of distilled and chromatographed product 2,6%, b.p. 205–215°/0.25 torr. IR ($CCl_4$), 1755 $cm^{-1}$. NMR ($CDCl_3$), $\delta$ 7,32 (s, 10H), 4,27, 4,47, 4,58 and 4,78 (AB system, 2H), 4,48 (s, 2H), 3,6–4,3 (broad, 2H), 2,4–2,9 (broad, 2H), 1,5–2,3 (broad, 6H). MS 336 ($M^+$, 0.5), 228 ($M^+$—$PhCH_2OH$, 5), 91 (100). (Found: C, 78,64%; H, 7,17. $C_{22}H_{24}O_3$ requires: C, 78,54%; H, 7,19%).

*Separation of stereoisomers*. Mixtures of stereoisomers were separated by column chromatography using 0.5% substrate/$SiO_2$ and eluting with mixtures hexane/ether.

(1*R*,2*R*,4*S*,5*S*)-2,4-*Dimethoxybicyclo*[3.2.1]*octan*-8-*one*, **4a**, IR ($CCl_4$), 1740 $cm^{-1}$. NMR ($CDCl_3$), $\delta$ 3,38 (broad, 2H), 3,28 (s, 6H), 2,58 (broad, 2H), 1,3–2,3 (broad, 6H). MS 184 ($M^+$: 7), 152 ($M^+$—MeOH, 63), 101 (MeO—$\overset{+}{C}H$—CH=CH—OMe, 100), 71 (MeO—$\overset{+}{C}H$—CH=$CH_2$, 55). (Found: C, 64, 18%; H, 8,91. $C_{10}H_{16}O_3$ requires: C, 65, 19%; H, 8,75%).

(1*R*,2*R*,4*S*,5*S*)-2,4-*Diethoxybicyclo*[3.2.1]*octan*-8-*one*, **4b**, IR ($CCl_4$), 1740 $cm^{-1}$. NMR ($CDCl_3$), $\delta$ 3,3-3,7 (broad, 6H), 2,5 (broad, 2H), 1,5–2,3 (broad, 6H), 1,15 (t, J = 6.5 Hz, 6H). MS 212 ($M^+$, 4), 166 ($M^+$—EtOH, 48), 129 (EtO—$\overset{+}{C}H$—CH=CH—OEt, 100), 101 (EtO—$\overset{+}{C}H$—CH=CH—OH, 41), 85 (EtO—$\overset{+}{C}H$—CH=$CH_2$, 67) (Found: C, 67,90%; H, 9,44. $C_{12}H_{20}O_3$ requires: C, 67,89%; H, 9,50%).

(1*RS*,2*RS*,4*RS*,5*SR*)-2,4-*Dimethoxybicyclo*[3.2.1]*octan*-8-*one*, **5a**, IR ($CCl_4$), 1750 $cm^{-1}$. NMR ($CDCl_3$), $\delta$ 3,4–3,9 (broad, 2H), 3,33 (s, 3H), 3,30 (s, 3H), 2,60 (broad, 2H), 1,4–2,2 (broad, 6H). MS 184 ($M^+$, 3), 152 ($M^+$—MeOH, 32), 101 (MeO—$\overset{+}{C}H$—CH=CH—OMe, 100), 71 (MeO—$\overset{+}{C}H$—CH=$CH_2$, 45). (Found: C, 65,05%; H, 8,72. $C_{10}H_{16}O_3$ requires: C, 65,19%; H, 8,75%.

(1*RS*,2*RS*,4*RS*,5*SR*)-2,4-*Diisopropoxybicyclo*[3.2.1]-*octan*-8-*one*, **5c**, IR ($CCl_4$), 1755 $cm^{-1}$. NMR ($CDCl_3$), $\delta$ 3,3–4,2 (broad, 4H), 2,3–2,6 (broad, 2H), 1,3–2,2 (broad, 6H), 1,12 (d, J = 6 Hz, 12H). MS 240 ($M^+$, 2), 180 ($M^+$—i—PrOH, 42), 157 ($(CH_3)_2CHO—\overset{+}{C}—CH=CH—OCH(CH_3)_2$, 100), 115 ($(CH_3)_2CHO—\overset{+}{C}H—CH=CH—OH$, 76), 73 ($HO—\overset{+}{C}H—CH=CH—OH$, 41). (Found: C, 70,08%; H, 10,41. $C_{14}H_{24}O_3$ requires: C, 69,96%; H, 10,07%).

(1*R*,2*S*,4*R*,5*S*)-2,4-*Diisopropoxybicyclo*[3.2.1]*octan*-8-*one*, **6c**, IR ($CCl_4$), 1755 $cm^{-1}$. NMR ($CDCl_3$), $\delta$ 3,95 (broad, 2H), 3.71 (h, J = 6 Hz, 2H), 2,3–2,55 (broad, 2H), 1,5–2,2 (broad, 6H), 1,10 (d, J = 6 Hz, 12H). MS 240 ($M^+$, 3), 180 ($M^+$—i—PrOH, 41), 157 ($(CH_3)_2CHO—\overset{+}{C}H—CH=CH—OCH(CH_3)_2$, 90), 115 ($(CH_3)_2CHO—\overset{+}{C}H—CH=CH—OH$, 100), 73 ($HO—\overset{+}{C}H—CH=CH—OH$, 65), (Found: C, 70,02%; H, 10,23. $C_{14}H_{24}O_3$ requires: C, 69,96%; H, 10,07%).

*Acknowledgement*—A fellowship from "Ministerio de Educación y Ciencia" to C. Jaime is gratefully acknowledged.

We gratefully thank Dr. A. Virgili for mass spectra, R. Segura for recording NMR spectra and to M. Guerra for elemental analysis.

## REFERENCES

[1]In a preliminary test 2,4-dimethoxybicyclo[3.2.1]octane has been converted in 54% yield into *cis*-cyclopentane-1,3-dicarboxylic acid.

[2]1,3-Dialkoxy-1,3-dichloropropanes, **3**, have been prepared from 1,1,3,3-tetraalkoxypropanes by reaction with a mixture of $PCl_5$ and $POCl_3$ as described for **3a** and **3b**: T.V. Protopopova and A. P. Skoldinov, *Zh. Obschei. Khim.* **29**, 3982–7 (1959); *Chem. Abt.* **54**, 20869f. 1,1,3,3-Tetramethoxypropane and 1,1,3,3-tetraethoxypropane are commercial products, and the corresponding tetraisopropoxy- and tetrabenzyloxypropanes have been prepared by transacetalisation from 1,1,3,3-tetramethoxypropane and the corresponding alcohol catalyzed by *p*-TsOH.

[3]The method is a modification of the synthesis of bicyclo[4.2.1]non-3-en-9-one, W. Clark Still, *Synthesis* 453 (1976).

[4]For reviews on Lanthanide shifts reagents, see:
R. Ammon and R. D. Fischer, *Angew. Chem.* Internat. Edn. **11**, 675 (1972).
A. F. Cockerill, G. L. O. Davies, R. C. Harden and D. M. Rackham, *Chem. Rev.* **73**, 553 (1973).