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# STEREOSELECTIVE REDUCTION OF β-KETO ESTERS WITH ZINC BOROHYDRIDE. STEREOSELECTIVE SYNTHESIS OF ERYTHRO-3-HYDROXY-2-ALKYLPROPIONATES

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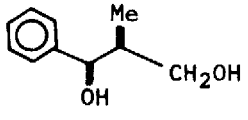
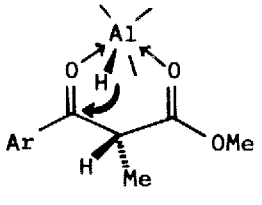
Erythro-3-hydroxy-2-alkylpropionates were prepared in high stereoselectivity and in high isolated yield by zinc borohydride reduction of the corresponding β-keto esters.

A method for the stereoselective synthesis of erythro-3-hydroxy-2-alkylpropionates (2) has been extensively studied in recent years[1] in connection with the synthetic works of macrolide or polyether antibiotics, since these moieties repeatedly appear in the framework of antibiotics such as erythromycin A. An effort to achieve this has been mainly focused on the stereocontrolled aldol condensation. We report here an alternative and highly stereoselective formation of these compounds by the reduction of the corresponding β-keto esters with zinc borohydride[2].

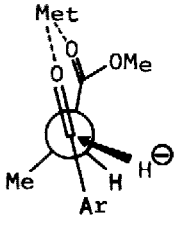
It has already been reported by Cancelll and Jacques[1a] that reduction of methyl 2-benzoyl propionate (1a) with $LiAlH_4$ produced erythro glycol (4) predominantly (erythro/threo ratio, 90/10) whereas reduction with $KBH_4$ afforded the threo derivatives (a mixture of glycol and hydroxy ester) as main products (erythro/threo ratio, 27/73)[3]. As an explanation for this discrepancy, they claimed that in the $LiAlH_4$ reduction the six-membered cyclic model (1) involving an aluminum hydride would initially be formed and a hydride attack subsequently




(4)




(1)

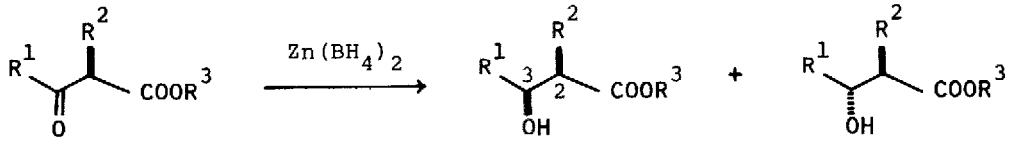



Met=$Li^+$, $Zn^{++}$

(11)

took place from the less hindered side affording erythro glycol as a major product, but in the $KBH_4$ reduction formation of such cyclic model can not be considered.

However, we thought that in the initial stage of the reduction, an association of a lithium cation to the carbonyl groups would be much rational than that of a negatively charged aluminum hydride anion. If this assumption is correct, even a metal borohydride could produce the erythro compounds when a counter metal possessed a highly coordinating ability to carbonyl oxygen (see, 11). The advantage of the use of a metal borohydride in this particular reduction is obvious because the desired erythro-hydroxy esters can be obtained directly from the β-keto esters which can, for example, be prepared from aldehydes and α-bromo esters by Reformatsky reaction followed by oxidation of the resulting secondary alcohols. Zinc borohydride was presumed to be ideally suited for this purpose. In fact, when β-keto esters (1) were treated with an excess of $Zn(BH_4)_2$ in ether for 10-30 min at 0 °C, erythro-3-hydroxy-2-alkyl esters (2a-e) were produced in high stereoselectivity and in high isolated yields except the case where $R^1$ was a flexible and bulky phenethyl group (1f ⟶ 2f). The results were summerized in Table 1.




(1) erythro (2) threo (3)

The stereostructures of 2a-e and 3a-e were determined based on the general rule[5] that $J_{2,3}$(threo) was larger than $J_{2,3}$(erythro) when the substituents on the vicinal carbon atoms, C-2 and C-3, were possible to form a hydrogen bonding and the size of $R^2$ was not so bulky (see, Table 2).

It is noteworthy that the present reaction can be carried out under standard procedure without any particular precaution. The simplicity in procedure would provide another advantage when this reaction was actually applied to the synthesis of macrolide antibiotics. Synthesis of erythronolide A starting from 2d and 2e is being undertaken in this laboratory.

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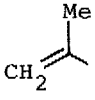
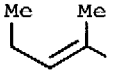
Table 1. Reduction of β-Keto Esters (1) with $Zn(BH_4)_2$

| | Keto esters (1) | | | Products | Combined |
|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | erythro (2) : threo (3) | isolated yield |
| a: | Ph | Me | Me | >99 : <1* | 98 % |
| b: | Ph | Et | Me | >99 : <1* | 98 % |
| c: | Ph  | Me | Me | 10 : 1* | 79 % |
| d: |  | Me | $CH_2Ph$ | >99 : <1** | 80 % |
| e: |  | Me | $CH_2Ph$ | >99 : <1** | 85 % |
| f: | $PhCH_2CH_2$ | Me | Me | 3 : 1*** | 98 % |

* Ratio after isolation.

** Ratio determined by NMR data.

*** See ref. 4.

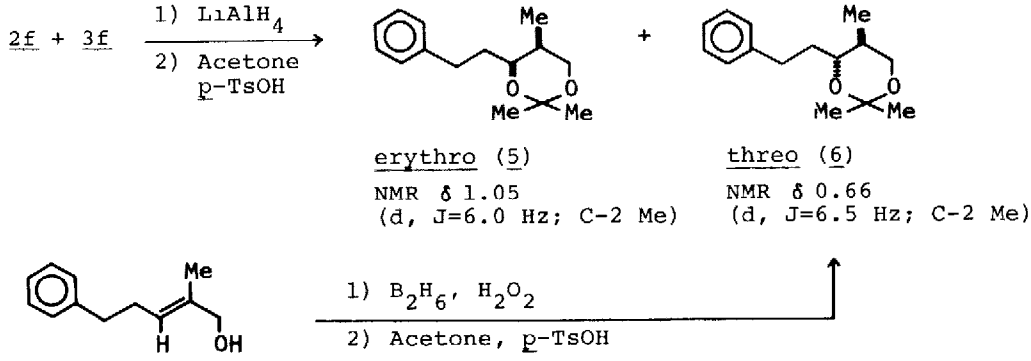
Table 2. NMR Data (in $CDCl_3$, 100 MHz) of C-3 H of 2 and 3

| | erythro (2) | threo (3) |
|---|---|---|
| a: | δ 5.00 (d, J=4.5 Hz)* | δ 4.70 (d, J=8.5 Hz)* |
| b: | δ 4.86 (d, J=6.0 Hz)* | δ 4.71 (d, J=8.5 Hz)* |
| c: | δ 4.54 (d,d,d, J=5.5, 4, 1 Hz) | δ 4.38 (t,d, J=7, 1 Hz) |
| d: | δ 4.36 (d, J=4.5 Hz) | δ 4.15 (d, J=8.5 Hz) |
| e: | δ 4.23 (d, J=6.0 Hz) | δ 4.10 (d, J=9.0 Hz) |

* See ref. 1a.

## References and Notes


1. a) J. Canceill, J.-J. Basselier, and J. Jacques, Bull. Soc. Chim. Fr., 1024 (1967); J. Canceill and J. Jacques, ibid., 2180 (1970). b) S. Yamada and K. Koga, Tetrahedron Lett., 1711 (1967). c) J. E. Dubois and P. Fellmann, Tetrahedron Lett., 1225 (1975). d) C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, and J. E. Sohn, J. Am. Chem. Soc., 101, 7077 (1979), and references cited therein. e) M. Hirama, D. S. Garvey, L. D.-L. Lu, and S. Masamune, Tetrahedron Lett., 3937 (1979), and references cited therein. f) R. W. Hoffmann and H.-J. Zeiss, Angew. Chem. Int. Ed. Engl., 18, 306 (1979). g) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, J. Am. Chem. Soc., 101, 259 (1979); M. R. Johnson, T. Nakata, and Y. Kishi, Tetrahedron Lett., 4343 (1979). h) D. A. Evans, E. Vogel, and J. V. Nelson, J. Am. Chem. Soc., 101, 6120 (1979). i) M. Isobe, M Kitamura, and T. Goto, Tetrahedron Lett., 3465 (1979). j) T. Hayashi, N. Fujitaka, T. Oishi, and T. Takeshima, Tetrahedron Lett., 303 (1980).
2. W. J. Gensler, F. Johnson, and A. D. B. Sloan, J. Am. Chem. Soc., 82, 6074 (1960).
3. Reduction of 1a with $Me_4NBH_4$ in THF-$H_2O$ gave erythro (2a) and threo (3a) hydroxy esters almost in the same ratio (28/72) (unpublished observation from this laboratory).
4. The ratio of 2f and 3f was determined based on the NMR data of C-2 methyl protons of erythro (5) and threo (6) isopropylidene derivatives derived from a mixture of 2f and 3f. The doublet appearing at δ 0.66 was assigned as that of 6 since the corresponding protons of the authentic threo derivative appear in the same position.




5. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, J. Am. Chem Soc., 95, 3310 (1973); A. Gaudemer, M. Golfier, A. Mandelbaum, and R. Parthasarathy, "Determination of Configurations by Spectrometric Methods", Vol. 1, Ed. by H. B. Kagan, Georg Thieme Publishers, Stuttgart, 1977, pp 69.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