1,4-Stereoselection by Sequential Aldol Addition–Claisen Rearrangement. Stereostructure of the C_{30} Diol from Messel Shale Kerogen[1]

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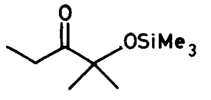
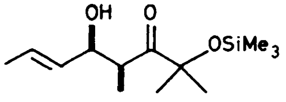
Diastereoisomeric amides (**9**) and (**10**) are prepared by stereoselective aldol addition, followed by Claisen rearrangement; isomer (**9**) has been employed to synthesize hydrocarbon (**14**) and thereby establish the stereostructure of the molecular fossil 13,16-dimethyloctacosane-1,28-diol.

It has recently been established that the aldol addition reaction can be used to achieve good 1,2-diastereoselection in the synthesis of β-hydroxy carbonyl compounds.[2] It is also known that the Claisen rearrangement of allyl vinyl ethers proceeds in many cases with faithful transfer of chirality from one centre to another.[3] We have previously shown that these two useful reactions may be effectively coupled to achieve good 1,5-diastereoselection.[4] In this paper we demonstrate that this strategy may also be employed to realize 1,4-diastereoselection. The technique is illustrated with a proof of relative stereochemistry of the C_{30} hydrocarbon prepared by Albrecht and coworkers from the diethers of 13,16-dimethyloctacosane-1,28-diol, isolated from Messel shale kerogen.[5]

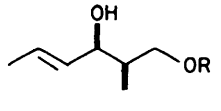
The β-hydroxy ketone (2), obtained in 97% yield from the reaction of the ketone (1)[6] with crotonaldehyde, was cleaved by periodic acid in tetrahydrofuran[7] to give a β-hydroxy acid which was reduced by lithium aluminium hydride to obtain the diol (3). The stereoselectivity of the original addition reaction was ≥50 : 1, as diol (3) and several of its derivatives were found to be homogeneous, within the limits of careful ^1H and ^{13}C n.m.r. analysis. The diastereoisomeric diol (6) was obtained by reaction of crotonaldehyde with the enolate of the ester (4),[8] followed by lithium aluminium hydride reduction of the resulting β-hydroxy ester (5). In the case of ester (4), the aldol addition reaction was less selective, and compound (5) was accompanied by 10% of its diastereoisomer. However, these isomers were separable by chromatography, thus allowing diol (6) to be obtained in good isomeric purity.



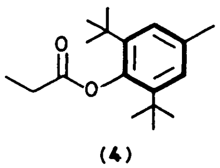
(1)



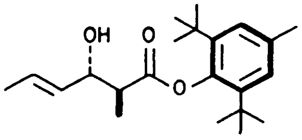
(2)



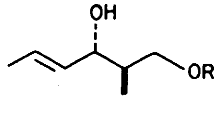
(3) R = H
(7) R = Bu^{t}Me$_2$Si



(4)



(5)



(6) R = H
(8) R = Bu^{t}Me$_2$Si

Diols (3) and (6) were converted into the t-butyldimethylsilyl ethers (7) and (8), which were each subjected to Eschenmoser's variant of the Claisen rearrangement.[9] Although the rearrangement showed the expected suprafacial stereoselectivity, both reactions gave rise to a mixture of unsaturated amides (9) and (10), the observed ratios being 9 : 1 from (7) and 1 : 19 from (8).† Since both products in each case were

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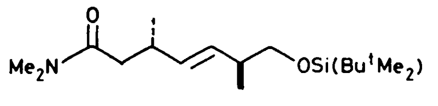
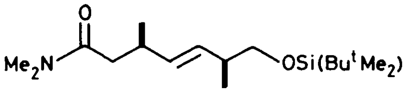
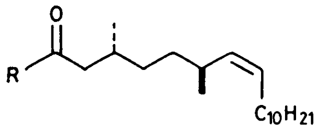
† The diastereoisomer ratios, as well as the identity of the minor isomers, were determined by ^{13}C n.m.r. spectroscopy and analytical h.p.l.c. on the analogous trityl ethers.



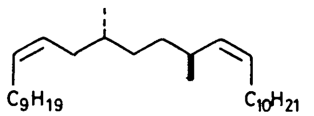
(9)



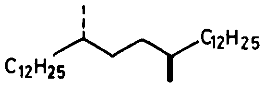
(10)



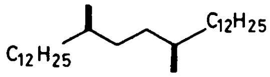
(11) R = Me$_2$N
(12) R = H



(13)



(14)



(15)

shown to have *E* double bonds, the minor products must have arisen from net antarafacial rearrangement, probably by a non-concerted, heterolytic mechanism.

Diimide reduction of (**9**), followed by desilylation and Parikh oxidation[10] afforded an aldehyde, which was condensed with undecylidenetriphenylphosphorane to obtain the unsaturated amide (**11**), primarily as the *Z* stereoisomer. Reduction of (**11**) with lithium in ammonia in the presence of Bu^{t}OH provided an aldehyde (**12**),‡ which was condensed with decylidenetriphenylphosphorane to obtain the diene (**13**), mainly as the *Z,Z* isomer. Catalytic hydrogenation of (**13**) over iridium on carbon provided *meso*-13,16-dimethyloctacosane (**14**). By capillary g.l.c., the synthetic hydrocarbon (**14**) was found *not* to be identical with the 13,16-dimethyloctacosane obtained by degradation of the C$_{30}$ diethers from Messel shale kerogen.[5]§ Thus, it follows that the naturally occurring C$_{30}$ diol has the configuration corresponding to (**15**) or its enantiomer.

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References

1 For part 17 of the series Acyclic Stereoselection, see C. H. Heathcock and J. Lampe, *J. Org. Chem.*, in the press.
2 See *inter alia* C. H. Heathcock, *Science*, 1981, **214**, 395.
3 S. J. Rhoads and N. R. Raulins, *Org. React.*, 1974, **22**, 1; F. E. Ziegler, *Acc. Chem. Res.*, 1977, **10**, 227.
4 C. H. Heathcock and E. T. Jarvi, *Tetrahedron Lett.*, 1982, **23**, 2825.
5 (a) B. Chappe, W. Michaelis, and P. Albrecht, in 'Advances in Organic Geochemistry 1979,' eds. A. G. Douglas and J. R. Maxwell, Pergamon, Oxford, 1980, p. 265; (b) B. Chappe, W. Michaelis, P. Albrecht, and G. Ourisson, *Naturwissenschaften*, 1979, **66**, 522; (c) B. Chappe, P. Albrecht, and W. Michaelis, *Science*, 1982, **217**, 65.
6 C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, 1980, **45**, 1066.
7 R. E. Ireland and J. Newbould, *J. Org. Chem.*, 1963, **28**, 23.
8 C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, *Tetrahedron*, 1981, **37**, 4087.
9 D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, 1969, **52**, 1030.
10 J. K. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.

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‡ It does not appear that this method has been widely used for the conversion of amides into aldehydes, although it has been reported that the technique is successful in special cases; see A. J. Birch, J. C. Craig, and M. Slaytor, *Aust. J. Chem.*, 1955, **8**, 512. In addition, electrolytic reduction of amides has been reported to afford aldehydes; R. A. Benkeser, H. Watanabe, S. J. Mels, and M. A. Sobel, *J. Org. Chem.*, 1970, **35**, 1210.

§ The comparison was made in Strasbourg by Drs. Albrecht and Chappe. The comparison was carried out indirectly, as follows. Synthetic (**14**) was shown to co-elute on a Pluronic F68 phase column with the more volatile component of a 1 : 1 mixture of (**14**) and (**15**), prepared as previously described, (ref. 5b) thus establishing the relative orders of elution of the two diastereoisomers. In contrast to the previous report (ref. 5b), the naturally derived hydrocarbon co-elutes with the *less volatile* isomer (P. Albrecht, personal communication, February 10, 1983).