J.C.S. Снем. Сомм., 1979

Asymmetric Syntheses from Terpene Alkanolamines. Formation of Optically Active 2-Methyloctanal

By A. I. MEYERS,* ZDENEK BRICH, and GARY W. ERICKSON

(Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523)

and SEAN G. TRAYNOR

(SCM Organic Chemicals, P.O. Box 389, Jacksonville, Florida 32201)

Summary Metallation and alkylation (MeI) of the aldimines derived from various terpene methoxy amines and octanal¹ produce, after hydrolysis, S(+)-2-methyloctanal in 11—75% enantiomeric excess.

Among the more successful asymmetric syntheses described recently is the alkylation of chiral imines via their lithio anions producing α -substituted ketones and aldehydes in



60—100% enantiomeric excess (e.e.).¹⁻³ The imines employed were derived from natural amino acids [e.g. from phenylalanine via (**6**)³ and from proline via (**7**)⁴] or synthetic amino acids, (**8**).⁵ All these syntheses depend upon a chelated metalloenamine (Scheme) to provide a rigid nucleophile with distinct topology. Recent studies have also shown that the geometry about the metalloenamine C-C bond (E vs. Z) is important for stereochemically biased alkylation.^{3a,6,7}



We now report that in addition to the above factors, the nature of the amino group, R_3CNH_2 or R_2CHNH_2 , is critical to the success of the asymmetric alkylation. The chiral alkanolamines (1a)--(5a) were transformed into their methyl ethers (1b)--(5b) (KH-MeI) and subjected to the

reaction sequence in the Scheme to give, in turn, compounds (9)—(12). The results of the asymmetric synthesis are given in the Table. It is seen that the secondary carbinamines (1b), (2b), and (5b) are more efficient chiral auxiliary groups than the tertiary carbinamines (3b) and (4b). The latter lead to 2-methyloctanal in poor enantiomeric purity.



Since previous work has shown that the skeletal structures of the chiral alkoxyamines (6)—(8) have little effect on the efficiency of the asymmetric synthesis^{3a,4,5,8} and since similar results were found by varying the alkyl group on the ether,^{3a} the nature of the amino group must be an important factor in the synthesis.



SCHEME. i, Octanal, ether, Na₂SO₄; ii, lithium 2,2,6,6-tetramethylpiperidide (LiTMP), tetrahydrofuran (THF), 0 °C; iii, MeI, -78 °C; iv, 25% aq. (±)-tartaric acid-THF (2:3). Hex = nhexyl.

The observation that chiral tertiary carbinamines are less effective in promoting biased alkylation may now be discussed in terms of the conformations (A) and (B) which allow the N-lone pair and N-vinyl group to lose their preference when \mathbb{R}^2 is methyl. Thus, the ground state energies for (A) and (B) become similar resulting in alkylation through both species and subsequent loss of stereoselectivity.

In summary, asymmetric C–C bond formation studies through the metalloenamines (10) must consider lone pair inversion as well as stereoselective deprotonation and rigid intermediates. Furthermore, it is remarkable that the c

Methoxyamines			2-Methyloctanal (12)			
Cpd.	B.p./°C (P/Torr)	[α] ₅₈₉ ^a /°	% Yield ^b	[α] ₅₈₉ ^c	% e.e. ^d	Configuration
(1b)	60-70 (0.15)	+31.7(4.8)	71	+15.6(10.3)	$55 \cdot 2$	S
(2b)	60—75 (O·15)	+28.1(4.9)	60	+21.6(4.7)	75.2	S
(3b)	120 - 125(0.5)	+46.6(1.86)	80	+ 6.8(7.4)	25.6	S
(4b)	6570 (0·15)	+48.2(7.3)	76	-2.3(10.3)	10.7	R
(5b)	118 - 120(0.2)	+34·4 (7·3)°	57	+14.8(6.8)	54.3	S

TABLE

^a Concentration in ethanol in parentheses. ^b Overall yield from (1b—5b). ^c Concentration in chloroform in parentheses. ^d % e.e. is based on max $[\alpha]_{589}$ 29.8° (ref. 3c) and ¹H n.m.r. data; *cf.* A. I. Meyers and Z. Brich, following communication. The % e.e. are corrected for the enantiomeric purities of (1a)(97%), (2a) (97%), (3a) (97%), (4a) (97\%), and (5a) (95—96\%).



skeletal structures of the chiral amino-ethers play an insignificant role in these processes in view of the belief that steric bulk was a prime requisite for success.

We thank the National Science Foundation for support, the Swiss Science Foundation for a Postdoctoral Fellowship to Z. B., and the N.I.H. for a Postdoctoral Fellowship to G. W. E.

(Received, 16th February 1979; Com. 157.)

15, 549. ⁵ S. Hashimoto and K. Koga, *Tetrahedron Letters*, 1978, 573, and references cited therein.

⁶ M. A. Hoobler, D. E. Bergbreiter, and M. Newcomb, J. Amer. Chem. Soc., 1978, 100, 8182; A. I. Meyers, E. Snyder, and J. Ackerman, ibid., p. 8186.

⁷ H. Albrecht, E. O. Duber, D. Enders, H. Eichenauer, and P. Weuster, *Tetrahedron Letters*, 1978, 3691; M. Newcomb and D. E. Bergbreiter, J.C.S. Chem. Comm., 1977, 486.
⁸ J. K. Whitesell and M. A. Whitesell, J. Org. Chem., 1977, 42, 377.