A New Enantioselective Synthesis of *trans* 2,5-Disubstituted Pyrrolidine Derivatives by Radical Cyclisation

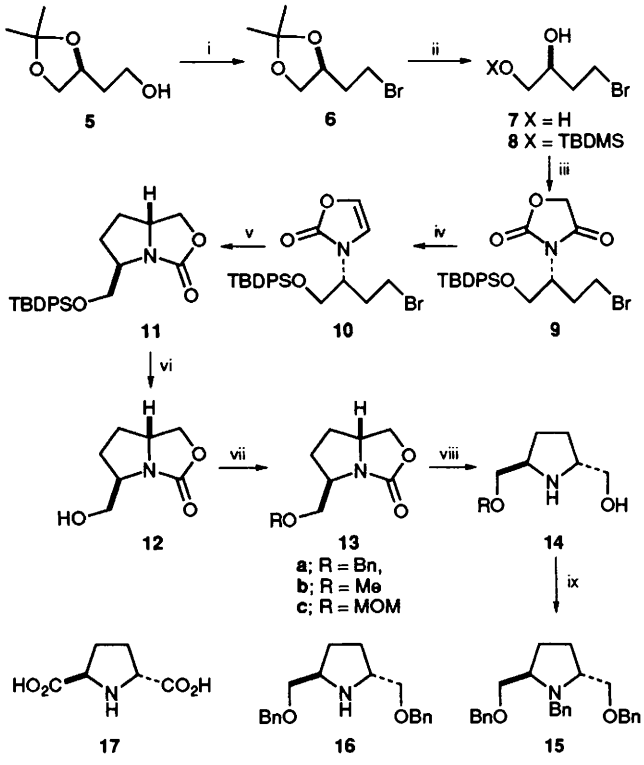
Yoko Yuasa, Jun Ando and Shiroshi Shibuya*

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

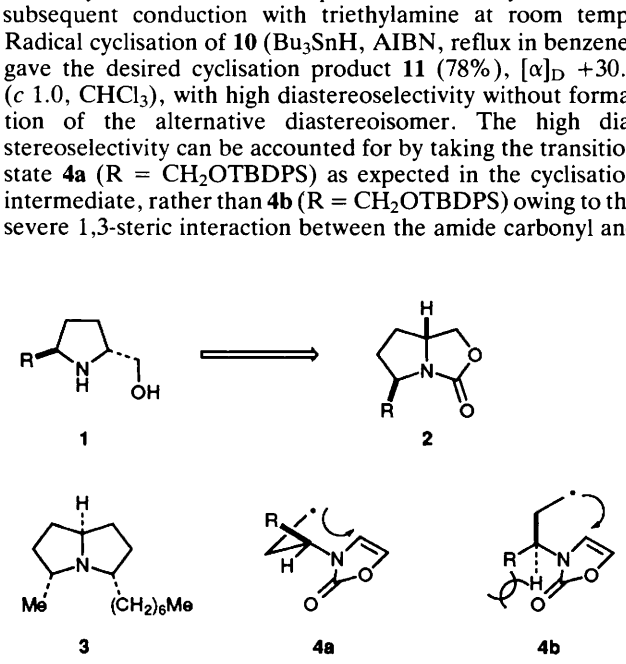
A new and highly enantioselective synthesis of *trans* 5-substituted 2-hydroxymethylpyrrolidine derivatives is achieved by intramolecular radical cyclization at the 4-position of $\Delta^{4,5}$-oxazolidin-2-one, which leads to C_2-symmetrical 2,5-dibenzyloxypyrrolidin-2-one.

Oxazolidinone ring has been recognized as a synthon for 2-amino alcohols or a protective form of 2-amino alcohols, since it can be cleaved easily under mild conditions to give 2-amino alcohols.[1] Thus, pyrrolooxazolidinone derivatives **2** can be considered as direct precursors for the chiral synthesis of 5-substituted 2-hydroxymethylpyrrolidines **1**. A number of applications have been found for type **1** compounds *e.g.* as a chiral auxiliary with a high level of asymmetric induction[2,3] and the enantiomer of **1** (R = Me) is known to be converted easily to pyrrolizidine alkaloids such as **3**.[4] New methodologies to get this type of pyrrolidine in the optical pure form are subject to continual refinement, because only a few approaches to their asymmetric synthesis, have been reported.[2,5] We investigated the facile and effective method for the synthesis of **2** (R = CH_2OH and Me) by application of intramolecular radical cyclisation. Our strategy is based on using $\Delta^{4,5}$-oxazolidine as the radical acceptor in the expectation that the cyclisation would proceed with high diastereoselectivity *via* the transition state **4a** rather than **4b** which contains considerably severe steric repulsion owing to the carbonyl and alkyl substituents.[6,7]

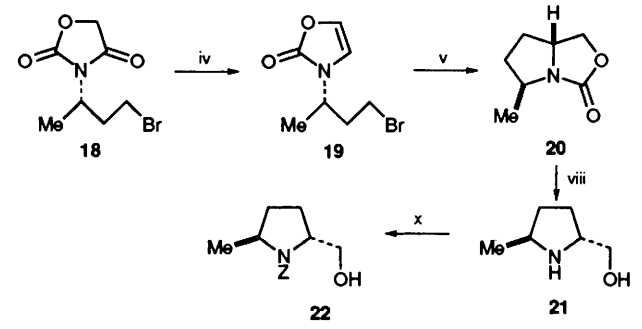
The acetonide **5**,[8] obtained from (*S*)-malic acid, was converted to the bromoacetonide **6**, $[\alpha]_D$ −27.9 (*c* 1.2, $CHCl_3$) through mesylation of the hydroxy group and subsequently bromination (LiBr, acetone). Cleavage of the dioxole ring of **6**, followed by selective protection of the resulting diol **7**, $[\alpha]_D$ −38.4 (*c* 1.6, $CHCl_3$), with *tert*-butyldiphenylsilyl (TBDPS) chloride gave **8**, $[\alpha]_D$ −10.7 (*c* 1.0, $CHCl_3$). *N*-Substitution of oxazolidine-2,4-dione was carried out using the Mitsunobu reaction [Ph_3P, ($Pr^iOCON{=})_2$ in THF] to yield **9**, $[\alpha]_D$ −11.2 (*c* 1.1, $CHCl_3$), which was converted easily to $\Delta^{4,5}$-oxazolidin-2-one **10**, $[\alpha]_D$ +19.1 (*c* 1.0, $CHCl_3$), through reduction with $NaBH_4$, followed by treatment with methanesulfonyl chloride in methylene chloride in the presence of triethylamine and subsequent conduction with triethylamine at room temp. Radical cyclisation of **10** (Bu_3SnH, AIBN, reflux in benzene) gave the desired cyclisation product **11** (78%), $[\alpha]_D$ +30.0 (*c* 1.0, $CHCl_3$), with high diastereoselectivity without formation of the alternative diastereoisomer. The high diastereoselectivity can be accounted for by taking the transition state **4a** (R = $CH_2OTBDPS$) as expected in the cyclisation intermediate, rather than **4b** (R = $CH_2OTBDPS$) owing to the severe 1,3-steric interaction between the amide carbonyl and the alkyl substituent. Desilylation, followed by *O*-benzylation of **12**,† $[\alpha]_D$ +45.8 (*c* 1,1, $CHCl_3$) (NaH, benzyl bromide, DMF) yielded **13a**, $[\alpha]_D$ +58.7 (*c*, 1.2 $CHCl_3$). Cleavage of **13a** (10% NaOH–EtOH, relux) afforded **14a**, $[\alpha]_D$ −12.5 (*c* 1.0, $CHCl_3$), conversion of which to C_2-symmetrical pyrrolidine **15** was achieved easily by conduction with benzyl bromide in the presence of NaH in DMF. The spectral data of **15**, $[\alpha]_D$ +69.5 (*c* 1.8, CH_2Cl_2) {lit.,[5] $[\alpha]_D$ +68.3 (CH_2Cl_2)}



Scheme 2 *Reagents and conditions*: i, $MeSO_2Cl$–Et_3N then LiBr, acetone, room temp., 1 h; ii, *p*-$MeC_6H_5SO_2Cl$, MeOH then TBDPSCl, 4-DMAP, Et_3N; iii, oxazolidine-2,4-dione, Ph_3P, ($Pr^iOOCON{=})_2$; iv, $NaBH_4$, MeOH then $MeSO_2Cl$, Et_3N; v, Bu_3SnH, AIBN, benzene, reflux; vi, 3 mol dm^{-3} HCl–THF = 1 : 4; vii **a**: NaH, BnBr, **b**: NaH, MeI, **c**: diisopropylethylamine, MOMCl; viii, 10% NaOH–EtOH; ix, NaH, BnBr, x, K_2CO_3, ZCl



Scheme 1



Scheme 3 *Reagents and conditions*: refer to Scheme 2

were identical with those in the literature. Since conversion of **15** to 2*R*,5*R*-dibenzyloxymethylpyrrolidine **16**[5] and *trans*-2,5-dicarboxylic acid **17**[9] was already known, this work should be widely applicable to a synthesis of a variety of C_2-symmetrical pyrrolidines. Furthermore, *O*-methylation of **12** (NaH, CH_3I, DMF) and *O*-methoxy methylation (Pr^i_2NEt, MOMCl) afforded **13b**, **c**, $[\alpha]_D$ +64.7 (*c* 1.6, $CHCl_3$), $[\alpha]_D$ +59.2 (*c* 1.2, $CHCl_3$), respectively. Ring cleavage of these (10% NaOH–EtOH, reflux) gave the corresponding *trans*-2,5-disubstituted pyrrolidine derivatives **14b**, **c**, $[\alpha]_D$ −14.3 (*c* 0.3, $CHCl_3$), $[\alpha]_D$ − 11.9 (*c* 2.5, $CHCl_3$), which would potentially be useful intermediates for the synthesis of the 2,5-disubstituted analogue and C_2-symmetrical derivatives.

This radical cyclisation was successively applied to the synthesis of the enantiomer of **3** (R = Me). *N*-Substituted oxazoline-2,4-dione **18**, obtained by condensation of oxazolidine-2,4-dione with (*R*)-2-hydroxybutyl bromide, was converted to **19** by the method as above. The radical cyclisation of **19** (Bu_3SnH, AIBN in benzene) gave **20**,‡ $[\alpha]_D$ +70.7 (*c* 0.9, $CHCl_3$), with high diastereoselectivity,[8] as an oil in 72% yield along with the formation of a small quantity of the debromination product. Ring cleavage of **20** (10% EtOH–NaOH) gave **21**, $[\alpha]_D$ −2.9 (*c* 0.1, MeOH), followed by benzyloxycarbonylation (ZCl, K_2CO_3) afforded **22**, $[\alpha]_D$ +43.8 (*c* 0.1, $CHCl_3$) {lit.,[4] the enantiomer of **22**, $[\alpha]_D$ −45.8 (*c* 3.98, $CHCl_3$)}. Since, the enantiomer of **22** was converted to the pyrrolidine alkaloid **3**,[4] this work constitutes a formal synthesis of the enantiomer of **22**.

Received, 1st October 1993, Com. 3/05906E

Footnotes

† Compound **12**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.46–1.62 (1H, m), 1.70–1.84 (1H, m), 2.05–2.18 (1H, m), 2.19–2.29 (1H, m), 3.50 (1H, dd, *J* 6.9, 11.3 Hz), 3.75 (1H, dd, *J* 3.6, 11.3 Hz), 3.90–4.06 (2H, m), 4.20 (1H, dd, *J* 4.1, 8.9 Hz), 4.55 (1H, dd, *J* 8.3, 8.9 Hz).

‡ Compound **20**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, d, *J* 6.5 Hz), 1.44–1.59 (2H, m), 2.01–2.07 (1H, m), 2.25–2.33 (1H, m), 3.90–4.00 (1H, m), 4.13 (1H, dd, *J* 3.6, 8.9 Hz), 4.46 (1H, dd, *J* 8.0, 8.9 Hz).

References

1 T. Yokomatsu, Y. Yuasa and S. Shibuya, *Heterocycles*, 1992, **33**, 1051, and references cited therein.
2 Y. Kawakami, Y. Ito, T. Kiatagawa, Y. Taniguchi, T. Katuski and M. Ymamaguchi, *Tetrahedron Lett.*, 1984, **25**, 857.
3 M. Uchikawa, T. Hanamoto, T. Katuski and M. Ymamaguchi, *Tetrahedron Lett.*, 1986, **27**, 4577; K. Fuji, M. Node and T. Kawabata, *Tetrahedron Lett.*, 1990, **31**, 3175; J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, 1977, **42**, 1663; J. K. Whitesell, M. A. Minton and K.-M. Chen, *J. Org. Chem.*, 1988, **53**, 5383; R. H. Schessinger and E. J. Iwanowicz, *Tetrahedron Lett.*, 1987, **28**, 2083.
4 S. Takano, S. Otaki and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1983, 1172; H. Takahata, H. Bandoh and T. Momose, *Tetrahedron: Asymmetery*, 1991, **2**, 351.
5 M. Marzi and D. Misiti, *Tetrahedron Lett.*, 1989, **30**, 6075.
6 Y. Yuasa, S. Kano and S. Shibuya, *Heterocycles*, 1991, **32**, 2311.
7 S. Kano, Y. Yuasa, K. Asami and S. Shibuya, *Chem. Lett.*, 1986, **5**, 735.
8 K. Mori, T. Takigawa and T. Matsuo, *Tetrahedron*, 1979, **35**, 933.
9 S. Takano, M. Moriya, Y. Iwabuchi and K. Ogasawara, *Tetrahedron Lett.*, 1989, **30**, 3805.