Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 8, pp. 1891-1894, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00245-6

Asymmetric Synthesis of (-)-(2*R*,6*R*)-2,6-Dimethylmorpholine

Emanuela Licandro,* Stefano Maiorana, Antonio Papagni, Mary Pryce,[1] Antonio Zanotti Gerosa[2]

Dipartimento di Chimica Organica e Industriale - Università degli Studi di Milano - via C.Golgi, 19, I-20133 Milano, Italy

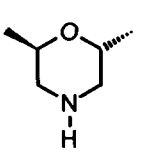
Sergio Riva

CNR-Istituto di Chimica degli Ormoni-via Mario Bianco, 9 , I-20131 Milano

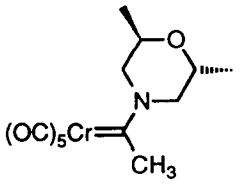
Abstract : The title compound was prepared efficiently by *O*-alkylation of (*R*)-ethyl lactate with the *O*-trifluoromethylsulphonyl derivative of (*S*)-ethyl lactate and further transformations of the two ester functionalities of the homochiral ether thus obtained.

The use of C_2 symmetric amines as chiral auxiliaries in asymmetric synthesis is widely documented in the literature.[3] The reason for this is that a reduced number of competing diastereomeric transition states are formed in the course of stereoselective synthesis. Generally most reports in the literature of these chiral auxiliaries deals with cyclic, secondary, α,α'-disubstituted amines. One of the reasons being, if the site of stereoselective transformation is located on the nitrogen atom, the presence of the two stereogenic centres in the α position can guarantee a high degree of stereoselectivity.[4]

As part of our work directed towards the synthesis and the study of the reactivity of Fischer type aminocarbene complexes,[5] we became interested in considering C_2 symmetric amines as chiral auxiliaries to be incorporated in these complexes. The additional interest for these kind of complexes is related to the fact that, conversely to other chiral amino carbene complexes, they exist as single isomers, in that the two rotamers arising from the hindered rotation around the carbene carbon atom and the nitrogen atom are identical. This peculiar characteristic leads to a useful simplification in the determination by ^{1}H NMR analysis of the stereoselection, when these complexes are used in stereoselective synthesis. Within this research work we found[6] that a very interesting and suitable amine was the (±)-*trans*-2,6-dimethylmorpholine **1**. Preliminary results from our laboratory [6] have shown that, despite the fact that the stereogenic centres are in the β position with respect to the nitrogen atom, the anion generated on the methyl group bonded to the carbene carbon atom of Fischer type carbene complex **2** gave the Michael addition on cyclic enones with a degree of diastereoselectivity analogous to that found by Wulff using a prolinol derivative as a chiral auxiliary.[7]



1

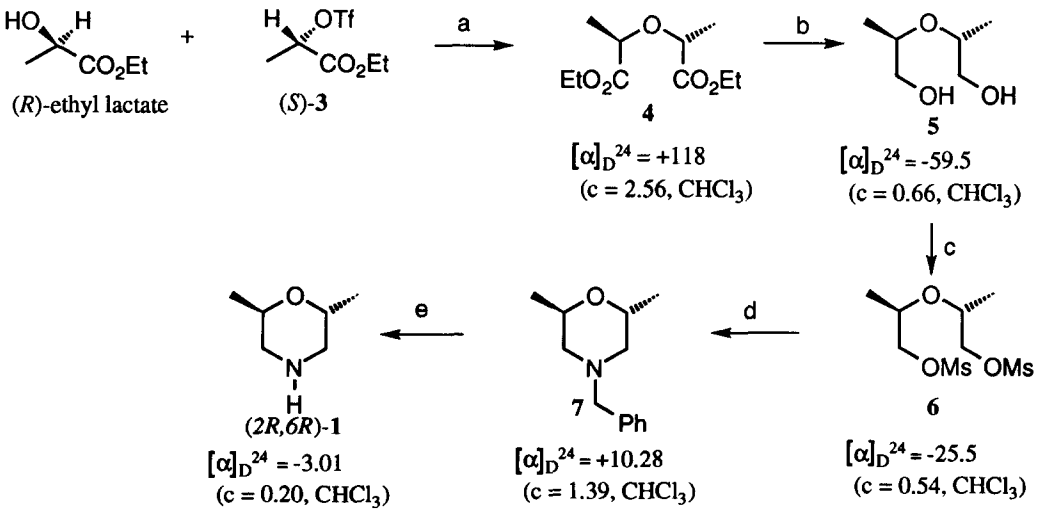


2

This preliminary encouraging result prompted us to study the procurement of the homochiral *trans*-2,6-dimethylmorpholine. This amine is commercially available as a mixture of *cis* and *trans* isomers (76.5% *cis* and 23.5% *trans*). The separation of this mixture into the *cis* and *trans* isomers has been reported[8,6]; however, quite surprisingly, the *trans*-2,6-dimethylmorpholine is not known in its enantiomerically pure form and, to the best of our knowledge, it has never been used as a chiral auxiliary.

The first approach we chose to obtain the homochiral amine was the separation into enantiomers through the fractional crystallization of diastereomeric salts obtained by the reaction of (±)-**1** with a variety of enantiomerically pure acids. However, the results with (*R*)-camphorsulfonic acid, (*R*)-mandelic acid and (*2R,3R*)-tartaric acid were so disappointing that we decided to develop a synthetic route to homochiral **1**. The key step of the synthesis was the formation of the ether **4**[9]; the chiral buildings blocks utilized were the commercially available (*R*)-ethyl lactate and the (*S*)-ethyl-2-[(trifluoromethylsulphonyl)oxy]propionate **3**[11] which were reacted in a nucleophilic substitution reaction (Scheme). In order to obtain stereochemically unambiguous S_N2 reaction, which was the prerequisite for a highly efficient stereoselective synthesis of ether **4**, we carefully chose the reaction conditions. The choice of solvent was particularly important as it can influence the mechanism of the nucleophilic substitution, leading to partial racemization if a borderline S_N2-S_N1 mechanism operates. We found that the best result in terms of chemical yield and diastereoselectivity was obtained by using a 4:1 mixture of *n*-pentane/1,2-dichloroethane as solvent and potassium carbonate as scavenger of the acid generated during the reaction.[13] The entire reaction sequence for the synthesis of (*R,R*)-(-)-**1** is reported in the following Scheme.

Scheme



Reagents and conditions: (a) K_2CO_3 (4.4 equiv), *n*-pentane/1,2-dichloroethane 4:1, 20 °C, 24 h, 89 %. (b) $LiAlH_4$, Et_2O, reflux, 30', 97 %. (c) MsCl (4 equiv), Py, 0 °C to 20 °C, 4 h, 94 %. (d) Benzylamine (9 equiv), dioxane, reflux, 85 %. (e) H_2, 5 % Pd/C, AcOH(1 equiv), MeOH, r.t., 16 h, 84%.

The diester **4** was recovered, after flash column chromatographic purification, in 89% yield,[14] together with a little amount of the corresponding optically inactive *cis* isomer. The reduction of **4** to the diol **5**[15] and the mesylation of **5** to **6**[16] were performed using standard reactions. The morpholine ring formation required some study; in fact, treatment of the dimesylate (-)-**6** with freshly distilled benzylamine at 80 °C for 32 hours[17] gave only a 30 % yield of (+)-**7**, but when the ring closure was performed with a nine fold excess of benzylamine in anhydrous dioxane as solvent at reflux for 15 hours, an 85 % yield of (+)-**7** was isolated after purification by column chromatography. The debenzylation of **7** was studied in two different conditions and optimized on the racemate *trans*-**7**. The first method employed was reduction using a $HCOONH_4$/Pd/C system in methanol as solvent at reflux temperature: however, although in some instancies we recovered the *trans*-(±)-**1** in high yield, the method was not easily reproducible; in fact, small variations in the reaction times led often to a mixture of 2,6-dimethylmorpholine and variable amounts of *N*-formylated derivative, which was not easy to separate or to transform into **1**. Therefore, the debenzylation on the homochiral (+)-**7** was most efficiently conducted with H_2 and 5% Pd/C in methanol/acetic acid at atmospheric pressure Spectroscopic and analytical data for compounds **5**, **7** and **1** were in accord with those reported for the corresponding racemates.[15,8,6]

None of the transformations from (+)-**4** to (-)-**1** (Scheme) involved modification of the stereocentres. The expected enantiomeric purity of the product was confirmed on **7** by chiral GLC analysis, by comparison with a base-line separated racemic sample (conditions: oven temperature from 80 °C to 110 °C with a heating rate of 0.1 °C/min).[19]

In conclusion, the synthesis of the (-)-(2*R*,6*R*)-2,6-dimethylmorpholine was accomplished in an efficient way from the commercially available (*R*)-ethyl lactate and *O*-triflate of the (*S*)-ethyl lactate, through a nucleophilic substitution which led to the formation of the key intermediate ether (+)-**4**. This compound was easily transformed into the desired (-)-(2*R*,6*R*)-**1** through an enantiospecific reaction sequence.

Additionally, the scope of the reaction for the generation of enantiomerically pure ethers such as (+)-**4** here reported will be further investigated, as well as the possibility of supressing completely the formation of the undesired *cis*-**4**.

ACKNOWLEDGEMENTS.

Authors wish to thank the M.U.R.S.T. (60 %), the C.N.R. of Rome and the European Community (HCM contract n°.ERBCHRXCT940501) for their financial support.

REFERENCES AND NOTES

1. Post-doctoral grant from EC (HCM programme, contract n°. CHRXCT940501).
2. Present adress: Institut de Chimie Minérale et Analytique, BCH, Université de Lausanne, CH-1015
3. Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. *Synthesis,* **1994**, 66 and references cited therein.
4. Chen, L.; Ghosez, L. *Tetrahedron Lett.* **1990**, *31*, 4467.
5. a) Lattuada, L.; Licandro, E.; Maiorana, S.; Papagni, A.; Zanotti Gerosa, A. *Synlett* , **1992**, 315;

b) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A.; Zanotti Gerosa, A. *Synlett*, **1994**, 677; c) Maiorana, S.; Papagni, A.; Licandro, E.; Persoons, A.; Clay, K.; Houbrechts, S.; Porzio, W. *Gazz. Chim. Ital.*, **1995**, accepted for publication.

6. Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A.; Zanotti Gerosa, A. *J. Organomet. Chem.*, **1995**, *486*, 279.
7. Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.*, **1993**, *115*, 4602.
8. a) Perrone, R.; Bettoni, G.; Tortorella, V. *Synthesis* , **1976**, 598; b) Leffer, M. T.; Volwiler, E. H. *J. Am. Chem. Soc.*,**1938**, *60*, 896.
9. Compound (+)-**4** has been reported in literature[10]; however in our hands the synthesis described always gave a complex mixture containing, mostly the racemic (±)- **4**, the *cis* isomer and others unidentified products.
10. Vieles, P. *Annales de Chemie* , **1935**, *3(11)*, 143.
11. *O*-Triflates of α-hydroxy esters have been used for the synthesis of α-hydroxylamino acid esters[12], however, to the best of our knowledge, no reaction with alcohols for the synthesis of enantiomerically pure ethers has hitherto been reported.
12. Feenstra, R. W.; Stokkinggreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron* , **1988**, *44*, 5583.
13. Under these conditions, *trans*-**4** was obtained in enantiomerically pure form, as determined by chiral GC. Conditions: CP-cyclodextrin-β-2,3,6-M 19 column (50 m, 0.25 mm ID, Chrompack); H_2 as carrier gas; oven temperature from 70 °C to 130 °C with a heating rate of 1 °C/min.
14. Colorless oil, ^{1}H-NMR ($CDCl_3$, 300 MHz); δ 1.25 (t, 6H, CH_2CH_3), 1.4 (d, 3H, $CHCH_3$), 4.05 (q, 2H, $CHCH_3$),4.17 (m, 4H, OCH_2). ^{13}C-NMR ($CDCl_3$, 300 MHz); δ 13.91 (q), 18.46 (q), 60.61 (t), 73.73 (d), 172.50 (s).
15. The optically inactive bis-[2-hydroxy-1-methyl-ethyl]ether **5** was already reported: *J. Am. Chem. Soc.* **1953**, *75*, 4357.
16. Yellow solid, m.p. 53 °C (*n*-heptane), ^{1}H-NMR ($CDCl_3$, 300 MHz); δ 1.2 (d, 6H, $CHCH_3$), 3.0 (s, 6H, SO_2CH_3), 3.86 (m, 2H, $CHCH_3$), 4.1 (m, 4H, CH_2OSO_2). ^{13}C-NMR ($CDCl_3$, 300MHz); 16.68 (q), 37.51 (q), 72.00 (d), 72.68 (t). Mass spectrum : 291 (M^+).
17. These conditions were reported for the synthesis of enantiomerically pure α,α'-disubstituted pyrrolidines[16].
18. Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755; Marzi, M.; Minetti, P.; Misiti, D. *Tetrahedron* **1992**, *48(46)*, 10127.
19. Similar attempts to obtain a base-line separation of racemic **1** were unsuccessful.

(*Received in UK* 27 *June* 1995)