

# Polymer-Aided Stereodivergent Synthesis (PASS): A New Concept for the Discrete Preparation of Optical Antipodes

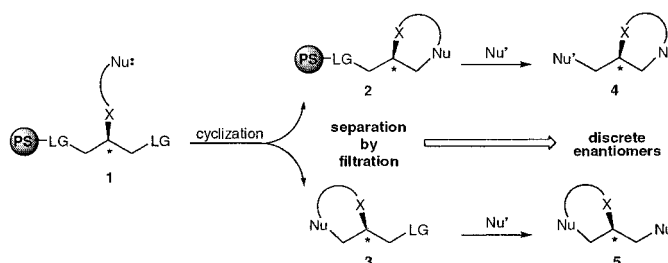
Peter ten Holte, Lambertus Thijs, and Binne Zwanenburg\*

Department of Organic Chemistry, NSR Institute for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

zwanenb@sci.kun.nl.

Received February 19, 2001

## ABSTRACT



A new concept for the discrete preparation of optical antipodes is reported. The approach makes use of a cyclization/cleavage procedure that has been applied to polymer-supported quasi-meso compound **1**, containing a polymeric leaving group and a regular leaving group. Two-directional cyclization leads to the formation and separation of quasi-enantiomers **2** and **3** simultaneously, with one being immobilized and one free in solution. Treatment of **2** and **3** with appropriate nucleophiles gives discrete enantiomers **4** and **5**.

The separation of enantiomeric species has been a challenge for chemists ever since Pasteur performed his “crystal picking” experiment in 1848.<sup>1</sup> Nowadays, it is becoming ever more important to be able to control the stereochemistry of chiral compounds, for example, in current drug research, where contamination of a sample with an undesired enantiomer can lead to fatal incidents. Many different approaches have been developed to ensure defined chirality of the products prepared. For instance, asymmetric syntheses using synthetic<sup>2</sup> or enzymatic<sup>2a,3</sup> catalysts as well as

numerous resolution methods<sup>2a,e–f,3,4</sup> have proved to be successful in providing enantiomerically pure target molecules.

In this paper, we report on a new concept that allows the discrete preparation of both quasi-enantiomers<sup>5</sup> of a chiral substance by making use of a polymeric support. The intention is to “racemize” a polymer-supported enantiopure compound, such as **1** (Scheme 1), by performing a two-directional cyclization reaction that leaves one quasi-enantiomer bound to the resin (**2**, route **a**) while the other one is in solution (**3**, route **b**), as illustrated in Scheme 1.

(1) (a) Pasteur, L. *Ann. Chim. Phys.* **1848**, 24, 442. (b) Pasteur, L. *Hebdomadaire des Seances Acad. Sci.* **1853**, 37, 162.

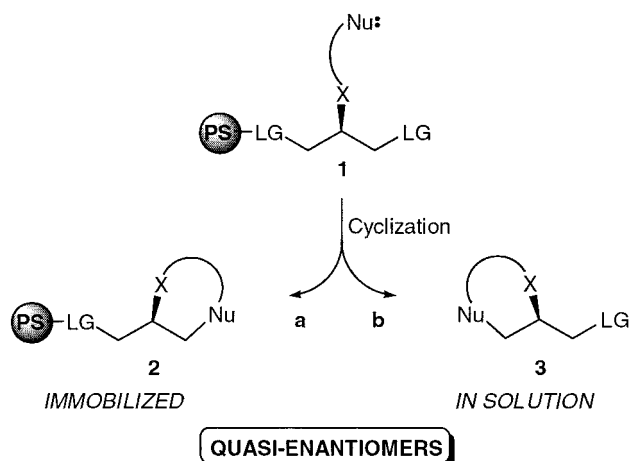
(2) (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, 40, 284. (b) Senkan, S. *Angew. Chem., Int. Ed.* **2001**, 40, 312. (c) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, 33, 382. (d) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Matsukawa, S. *Acc. Chem. Res.* **2000**, 33, 391. (e) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1059. (f) Brown, J. M. *Chem. Soc. Rev.* **1993**, 22, 25. (g) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, 92, 833.

(3) (a) Bakke, M.; Takizawa, M.; Sugai, T.; Ohta, H. *J. Org. Chem.* **1998**, 63, 6929. (b) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, 92, 1071.

(4) (a) Vries, T.; Wynberg, H.; van Echten, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. *Angew. Chem., Int. Ed.* **1998**, 37, 2349. (b) Vannieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, 115, 7864.

(5) According to the 1996 IUPAC recommendations, quasi-enantiomers are defined as “constitutionally different yet closely related chemical species MX and MY having the opposite chirality sense of the large common chiral moiety, M.”

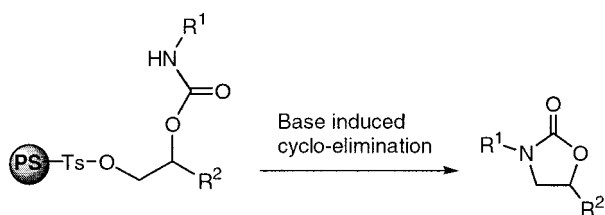
Scheme 1



System **1** consists of a central stereogenic carbon atom that has a nucleophilic group attached to it via a spacer and is flanked by two leaving groups that are connected to the chiral center by methylene units. The system is “quasi-meso” since one of the (technically identical) leaving groups is, in contrast to the other, bound to a polymeric backbone. An intramolecular nucleophilic cyclization can either substitute the polymeric leaving group or the nonpolymeric leaving group, resulting in a detached and a polymer-bound product, respectively. The quasi-enantiomeric products can be separated by filtration and converted into enantiomers by successive substitution of the unaffected leaving group. We have termed this approach polymer-aided stereodivergent synthesis (PASS). Thus, PASS allows the *discrete* preparation of quasi-enantiomers from enantiopure starting material in one step and gives access to the *enantiomers* by further functionalization.

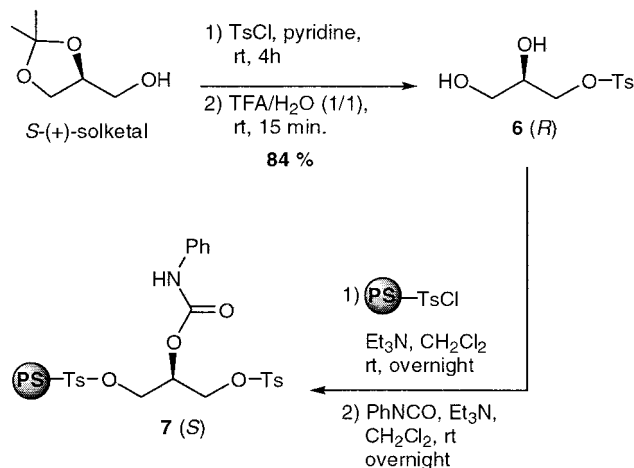
The strategy utilized to put the concept of PASS into practice is based on our earlier work on the application of immobilized arenesulfonate esters in the synthesis of a series of 3,5-disubstituted 1,3-oxazolidin-2-ones by means of solid-phase/activation cyclo-elimination (SP/ACE) methodology.<sup>6</sup> This approach employs 1,2-diols as the starting material and gives rise to a system that allows intramolecular cyclo-elimination in the last step of the synthetic sequence, yielding detached oxazolidinones of high purity as the cleavage products (Scheme 2).

Scheme 2



To prepare a substrate that is suitable for PASS, i.e., conceptually according to system **1** (Scheme 1), we replaced the 1,2-diol starting material by an enantiopure glycerol derivative. Thus, (*S*)-(+)-solketal (Scheme 3) was reacted

Scheme 3



with *p*-toluenesulfonyl chloride, and the arenesulfonate obtained was deketalized with trifluoroacetic acid in water. The resulting optically pure 1,2-diol **6**<sup>7,8</sup> was selectively attached with its primary alcohol function to polymer-bound arenesulfonyl chloride<sup>9</sup> and, subsequently, the secondary alcohol was converted into a carbamate by reaction with phenyl isocyanate to give quasi-meso system **7** with the *S*-configuration (Scheme 3).

Quasi-meso system **7** was then treated with DBN (2 equiv) in dichloromethane to induce the cyclo-elimination reaction. Cyclization route **a** provided polymer-bound oxazolidinone **8**, while elimination via route **b** gave quasi-enantiomeric oxazolidinone **9** in solution (Scheme 4).

Along with the tosylate-substituted oxazolidinone **9**, a considerable amount of chloride-substituted oxazolidinone **12** (Nu = Cl) was also obtained via route **b** (ratio **9/12** = 1/2, according to GC-MS analysis). Substitution of the tosylate with chloride probably had already occurred during the coupling reaction of the glycerol derivative **6** with the polymeric support whereby triethylammonium chloride is formed. There was no need to separate the chloride analogue **12** from oxazolidinone **9** because, where appropriate, both the tosylate and chloride leaving groups are readily substi-

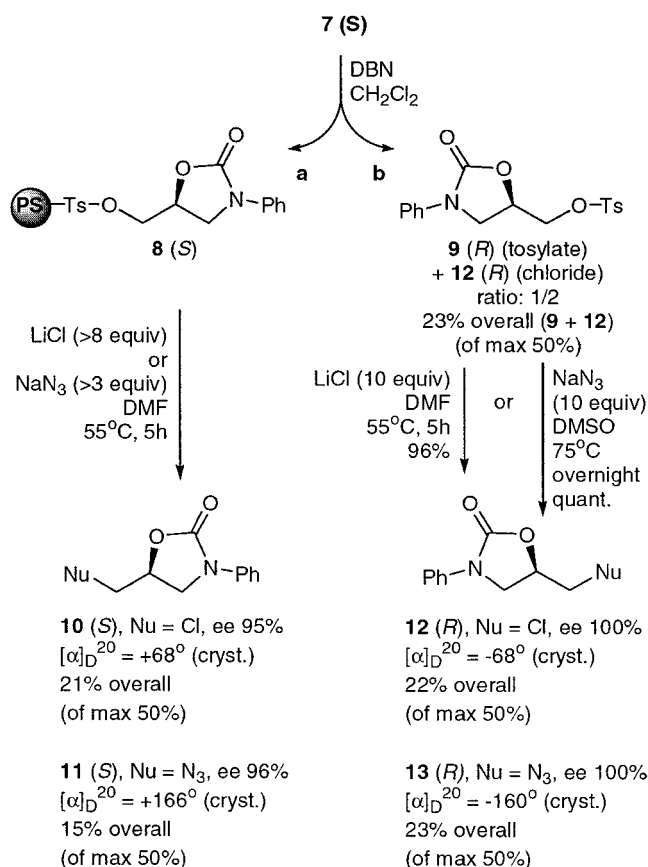
(6) ten Holte, P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, 39, 7407.

(7) Compound **6**: mp 57–59 °C;  $[\alpha]_D^{20} = -9.5^\circ$  ( $c = 5.5$ , methanol); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.42 (s, 3H, CH<sub>3</sub>), 3.55 (dd, 1H, part of ABX,  $J_{AB} = 11.6$  Hz,  $J_{BX} = 5.8$  Hz), 3.64 (dd, 1H, part of ABX,  $J_{AB} = 11.6$  Hz,  $J_{AX} = 3.8$  Hz), 3.74 (bs, 2H), 3.93 (m, 1H), 4.03 (m, 2H), 7.34 (d, 2H,  $J = 8.2$  Hz), 7.78 (d, 2H,  $J = 8.3$  Hz) ppm. Melting point and spectral data are in agreement with those reported: Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, 43, 4876.

(8) Unreacted 1,2-diol **6** was readily recovered by filtration and subsequent flash column chromatographic purification (ethyl acetate/hexane = 1/1, v/v, 250 mL followed by ethyl acetate) of the concentrated filtrate.

(9) PS-TsCl, 1.34 mequiv/g, Argonaut Technologies Inc.

Scheme 4



tuted in the subsequent reaction. As the formation of oxazolidinone **12** had taken place spontaneously, chloride was the logical nucleophile of choice in the reaction of **8** and **9** in order to prepare optical antipodes **10**<sup>10</sup> and **12**,<sup>11</sup> respectively. Thus, polymer-bound oxazolidinone **8** and its quasi-enantiomer **9** were treated with lithium chloride (8

equiv, based on maximum theoretical loading) in DMF to give enantiomers **10** and **12**. Oxazolidinone **12** thus obtained is optically pure by chiral HPLC (Chiralcel OD, ee = 100%), with an optical rotation of  $-68^\circ$  ( $c = 0.33$ , ethanol), whereas crude product **10** was formed in an ee of 95% (Chiralcel OD, hexane/isopropyl alcohol = 80/20). Crystallization of **10** (ethanol) gave the optically pure enantiomer with an optical rotation of  $+68^\circ$  ( $c = 0.34$ , ethanol). Another nucleophile that was examined was azide. Thus, the azide-substituted optical antipodes **11**<sup>12</sup> and **13**<sup>13,14</sup> were prepared by reaction of quasi-enantiomers **8** and **9** (+ compound **12**) with sodium azide (3 and 10 equiv, respectively) producing enantiomer **13** in optically pure form directly (Chiralcel OD, ee = 100%,  $[\alpha]_{\text{D}}^{20} = -160^\circ$ ,  $c = 0.30$ , ethanol) and enantiomer **11** in 96% ee (Chiralcel OD, hexane/isopropyl alcohol = 80/20). Crystallization of **11** furnished optically pure product ( $[\alpha]_{\text{D}}^{20} = +166^\circ$ ,  $c = 0.30$ , ethanol).

It is worth noting that the reactions of the nucleophiles with tosylate **9** and chloride **12** in solution do not lead to racemized products, whereas the products that arise from polymer-supported tosylate **8** seem to have racemized slightly.

In conclusion, we have successfully applied the new concept of *polymer-aided stereodivergent synthesis* (PASS) in the discrete formation of antipodal oxazolidinones.

**Supporting Information Available:** Experimental procedures for the preparation of compounds **6** and **7** and for the cyclization of **7** to give the quasi-enantiomeric species **8** and **9**. General procedure for the conversion of quasi-enantiomer **8** into the corresponding enantiomers **10** and **11**. Procedure for the conversion of the mixture of quasi-enantiomer **9** and compound **12** into enantiomers **12** and **13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL015723H

(10) Compound **10**: mp  $132^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.75 (dd, part of ABX,  $J_{\text{AB}} = 11.6$  Hz,  $J_{\text{BX}} = 6.6$  Hz, 1H), 3.80 (dd, part of ABX,  $J_{\text{AB}} = 11.6$  Hz,  $J_{\text{AX}} = 4.2$  Hz, 1H), 3.97 (dd, part of ABX,  $J_{\text{AB}} = 9.2$  Hz,  $J_{\text{BX}} = 5.7$  Hz, 1H), 4.18 (t, part of ABX,  $J_{\text{AB}} = J_{\text{AX}} = 9.0$  Hz, 1H), 4.88 (m, part of ABX, 1H), 7.16 (t,  $J = 7.4$  Hz, 1H), 7.39 (t,  $J = 8.0$  Hz, 2H), 7.55 (d,  $J = 8.1$  Hz, 1H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  44.47, 48.15, 70.80, 118.31, 124.38, 129.13, 137.76, 153.87.

(11) Compound **12**: mp  $132^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.74 (dd, part of ABX,  $J_{\text{AB}} = 11.6$  Hz,  $J_{\text{BX}} = 6.5$  Hz, 1H), 3.80 (dd, part of ABX,  $J_{\text{AB}} = 11.6$  Hz,  $J_{\text{AX}} = 4.2$  Hz, 1H), 3.97 (dd, part of ABX,  $J_{\text{AB}} = 9.2$  Hz,  $J_{\text{BX}} = 5.7$  Hz, 1H), 4.18 (t, part of ABX,  $J_{\text{AB}} = J_{\text{AX}} = 9.0$  Hz, 1H), 4.87 (m, part of ABX, 1H), 7.16 (t,  $J = 7.4$  Hz, 1H), 7.39 (t,  $J = 8.0$  Hz, 2H), 7.55 (d,  $J = 7.8$  Hz, 1H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  44.48, 48.15, 70.80, 118.32, 124.39, 129.13, 137.76, 153.86 ppm.

(12) Compound **11**: mp  $75-77^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.60 (dd, part of ABX,  $J_{\text{AB}} = 13.2$  Hz,  $J_{\text{BX}} = 4.5$  Hz, 1H), 3.70 (dd, part of ABX,  $J_{\text{AB}} = 13.2$  Hz,  $J_{\text{AX}} = 4.7$  Hz, 1H), 3.88 (dd, part of ABX,  $J_{\text{AB}} = 9.0$  Hz,  $J_{\text{BX}} = 6.2$  Hz, 1H), 4.11 (t, part of ABX,  $J_{\text{AB}} = J_{\text{AX}} = 9.0$  Hz, 1H), 4.79 (m, part of ABX, 1H), 7.16 (t,  $J = 7.4$  Hz, 1H), 7.39 (t,  $J = 8.0$  Hz, 2H), 7.54 (d,  $J = 7.8$  Hz, 1H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  47.44, 53.03, 70.54, 118.27, 124.34, 129.13, 137.83, 153.90 ppm.

(13) Compound **13**: mp  $76-78^\circ\text{C}$ ;  $^1\text{H}$  NMR is identical to that of **11**.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  47.44, 53.04, 70.54, 118.28, 124.35, 129.14, 137.84, 153.93 ppm.

(14) Optical rotation,  $^1\text{H}$  NMR, and melting point of **13** are in agreement with those reported: Gregory, W. A.; Brittelli, D. R.; Wang, C.-L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Barthohomew, P. T.; Slee, A. M.; Forbes, M. J. *Med. Chem.* **1989**, *32*, 1673.