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

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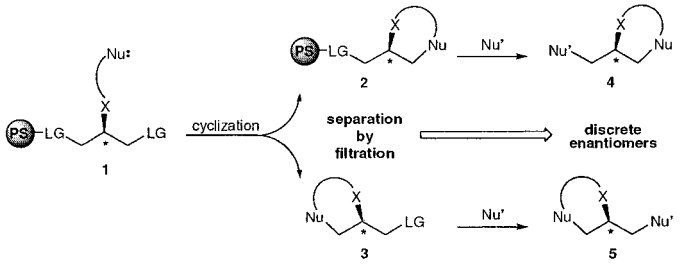
ABSTRACT



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.[1] 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[2] or enzymatic[2a,3] catalysts as well as numerous resolution methods[2a,e−f,3,4] 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[5] 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. *Hebd. 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."

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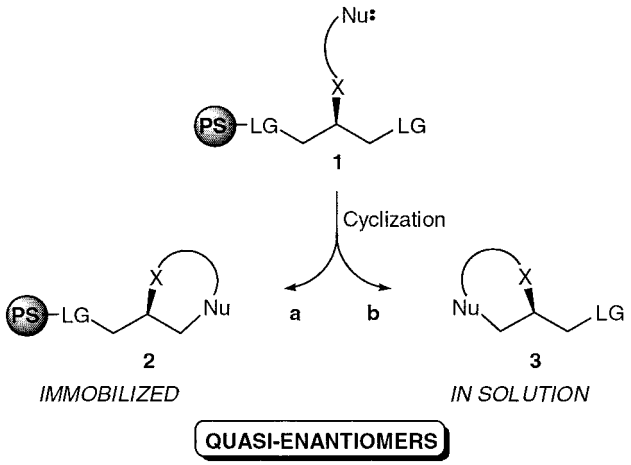
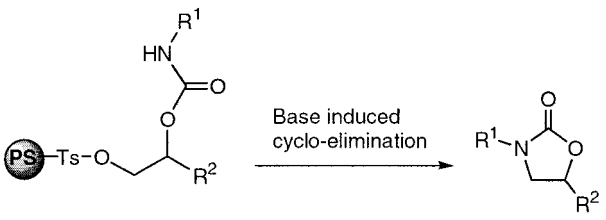
Scheme 1



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.

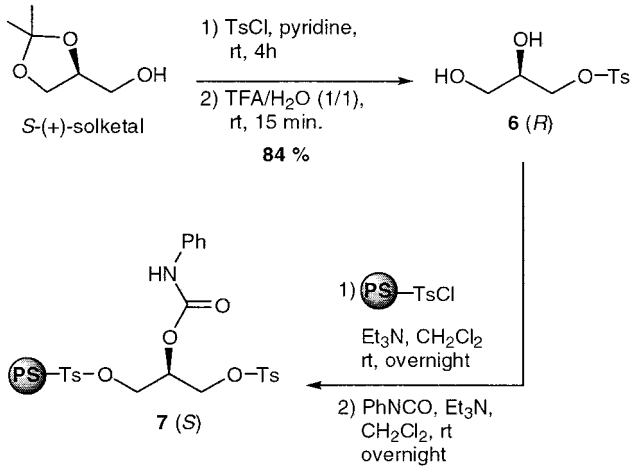
The strategy utilized to put the concept of PASS into practice is based on our earlier work on the application of immobilized arenesulfonate esters in the synthesis of a series of 3,5-disubstituted 1,3-oxazolidin-2-ones by means of solid-phase/activation cyclo-elimination (SP/ACE) methodology.[6] This 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**[7,8] was selectively attached with its primary alcohol function to polymer-bound arenesulfonyl chloride[9] 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 oxazolidininone **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-

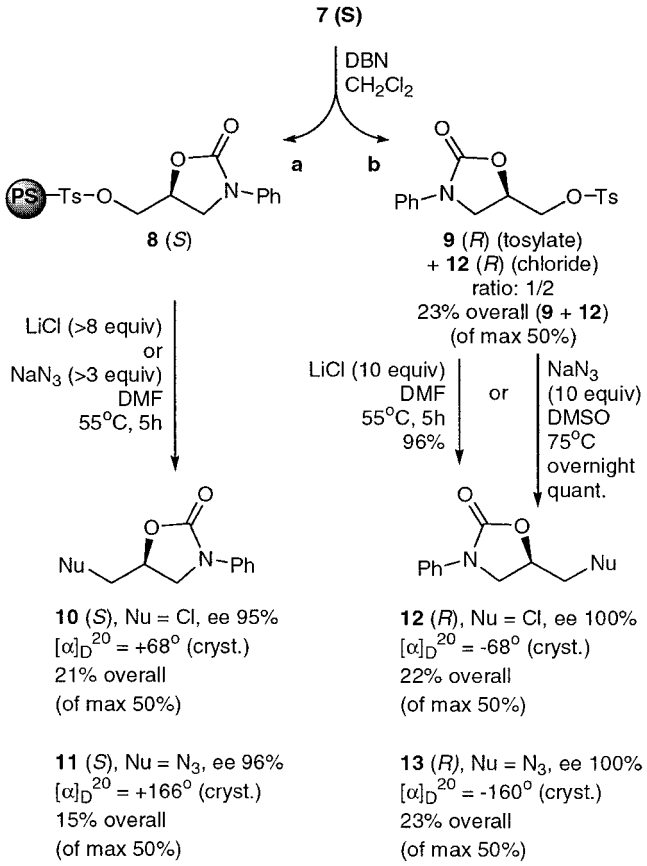
(6) ten Holte, P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 7407.

(7) Compound **6**: mp 57−59 °C; $[\alpha]^{20}_D = -9.5°$ (c = 5.5, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H, CH_3), 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**[10] and **12**,[11] 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° (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° (c = 0.34, ethanol). Another nucleophile that was examined was azide. Thus, the azide-substituted optical antipodes **11**[12] and **13**[13,14] 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%, $[\alpha]^{20}_D$ = −160°, c = 0.30, ethanol) and enantiomer **11** in 96% ee (Chiralcel OD, hexane/isopropyl alcohol = 80/20). Crystallization of **11** furnished optically pure product ($[\alpha]^{20}_D$ = +166°, 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 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.75 (dd, part of ABX, J_{AB} = 11.6 Hz, J_{BX} = 6.6 Hz, 1H), 3.80 (dd, part of ABX, J_{AB} = 11.6 Hz, J_{AX} = 4.2 Hz, 1H), 3.97 (dd, part of ABX, J_{AB} = 9.2 Hz, J_{BX} = 5.7 Hz, 1H), 4.18 (t, part of ABX, J_{AB} = J_{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}C NMR (75 MHz, $CDCl_3$) δ 44.47, 48.15, 70.80, 118.31, 124.38, 129.13, 137.76, 153.87.

(11) Compound **12**: mp 132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.74 (dd, part of ABX, J_{AB} = 11.6 Hz, J_{BX} = 6.5 Hz, 1H), 3.80 (dd, part of ABX, J_{AB} = 11.6 Hz, J_{AX} = 4.2 Hz, 1H), 3.97 (dd, part of ABX, J_{AB} = 9.2 Hz, J_{BX} = 5.7 Hz, 1H), 4.18 (t, part of ABX, J_{AB} = J_{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}C NMR (75 MHz, $CDCl_3$) δ 44.48, 48.15, 70.80, 118.32, 124.39, 129.13, 137.76, 153.86 ppm.

(12) Compound **11**: mp 75−77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.60 (dd, part of ABX, J_{AB} = 13.2 Hz, J_{BX} = 4.5 Hz, 1H), 3.70 (dd, part of ABX, J_{AB} = 13.2 Hz, J_{AX} = 4.7 Hz, 1H), 3.88 (dd, part of ABX, J_{AB} = 9.0 Hz, J_{BX} = 6.2 Hz, 1H), 4.11 (t, part of ABX, J_{AB} = J_{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}C NMR (75 MHz, $CDCl_3$) δ 47.44, 53.03, 70.54, 118.27, 124.34, 129.13, 137.83, 153.90 ppm.

(13) Compound **13**: mp 76−78 °C; ^{1}H NMR is identical to that of **11**. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.44, 53.04, 70.54, 118.28, 124.35, 129.14, 137.84, 153.93 ppm.

(14) Optical rotation, ^{1}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.