Synthesis of the Alkaloid Natural Products (+)-Plicane and (−)-Obliquine, Using Polymer-Supported Reagents and Scavengers†

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Two new naturally occurring amaryllidaceae alkaloids have been synthesized, using a divergent approach facilitated by the use of polymer-supported reagents and scavengers.

Introduction

The amaryllidaceae alkaloids have been the recipients of considerable synthetic interest, because of their extensive structural diversity and broad biological activity.[1,2] Our group has already reported on the synthesis of a selection of these compounds that have been prepared using a suite of solid-supported reagents,[3−5] to facilitate more-efficient synthesis.[6] We were particularly interested in the molecular architecture of (+)-plicamine (**1**) (Figure 1), which is the first member of a new *bis*-nitrogen-containing family of alkaloids to be isolated[5] from extracts of the Turkish *Galanthus plicatus* (subsp. Byzantinus).[8] Following our synthesis of this molecule,[6b,c] we became aware of a subsequent study by the same group in which a structurally related alkaloid (+)-plicane (**2**) was characterized.[9] In addition, an investigation into a related amaryllidaceae *Cyrtanthus obliquus*,[10] which is indigenous to the Cape and KwaZulu Natal provinces of South Africa, provided a third member of the series, namely, (−)-obliquine (**3**).[11] It would appear from the structural similarities that the compounds of the plicamine subgroup can exhibit both configurations at C-3. We anticipated that the synthetic pathway in our original synthesis of plicamine[6b,c] would allow us to access these two new natural products and also permit the preparation of their two epimeric derivatives (**4** and **5**) in a rapid and divergent fashion. This would also assist structural assignment, because ambiguity could easily exist in the series and in addition to providing new molecules for biological screening.

Therefore, starting from the common intermediate **6**,[6b,c] two parallel pathways were followed (Scheme 1). Route A involved the initial conversion of the C-3 alcohol to the resulting mesylate, followed by stereocontrolled nucleophilic inversion with methanol to yield **7** in high yield. Alternatively, route B furnished the C-3 methoxy epimer **8** via methylation using trimethylsilyl diazomethane (TMS−CHN_2) and an immobilized sulfonic acid catalyst also in excellent yield. The trifluoroacetate groups from both compounds **7** and **8** could be efficiently cleaved under basic conditions when facilitated by flash microwave heating[12] to give the corresponding amines **9** and **10**, respectively. Direct oxidation of amine **9** with cerium ammonium nitrate absorbed on silica then gave a clean transformation to the imine, (+)-plicane (**2**). In an identical manner, 3-*epi*-plicane (**4**) could be prepared from the matching amine **10**, using the same reagent.

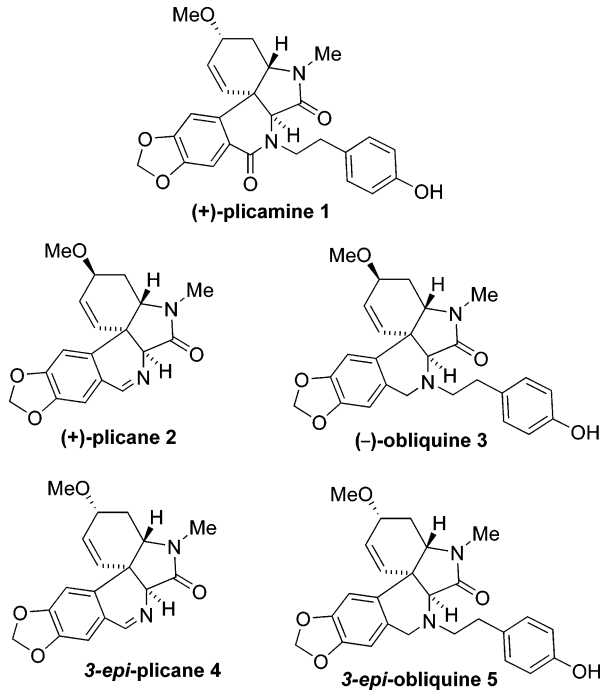

Figure 1. Schematic of the plicamine family of dinitrogenous amaryllidaceae alkaloids **1**−**5**.

Branching in a different direction from the same two amines **9** and **10** permitted synthesis of the products (−)-obliquine (**3**) and *epi*-obliquine (**5**) (subsequently leading to plicamine (**1**)). *N*-Alkylation with the alkyl bromide **11** promoted by an immobilized carbonate base, followed by scavenging the reaction mixture with an aminothiol resin, proved to be an efficient sequence. The natural products were identical to the reported authentic material.

Conclusion. In conclusion, a general and straightforward synthesis design has led to the preparation of a range of naturally occurring amaryllidaceae alkaloids. In addition, we have prepared two structural analogues (**4** and **5**) that possess the required functional components and stereochemistry of products that are likely to be isolated members of the plicamine family in the future. The synthesis strategy that is applied relies on the application of solid-supported reagents to provide products and intermediates in high yield and purity, without the need to resort to extensive chromatographic purification following each synthesis step.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker Advance DPX-400 spectrometer, with residual chloroform as the

† This paper is dedicated to Dave Sherrington, a good friend and fine scientist on the occasion of his 60th birthday.

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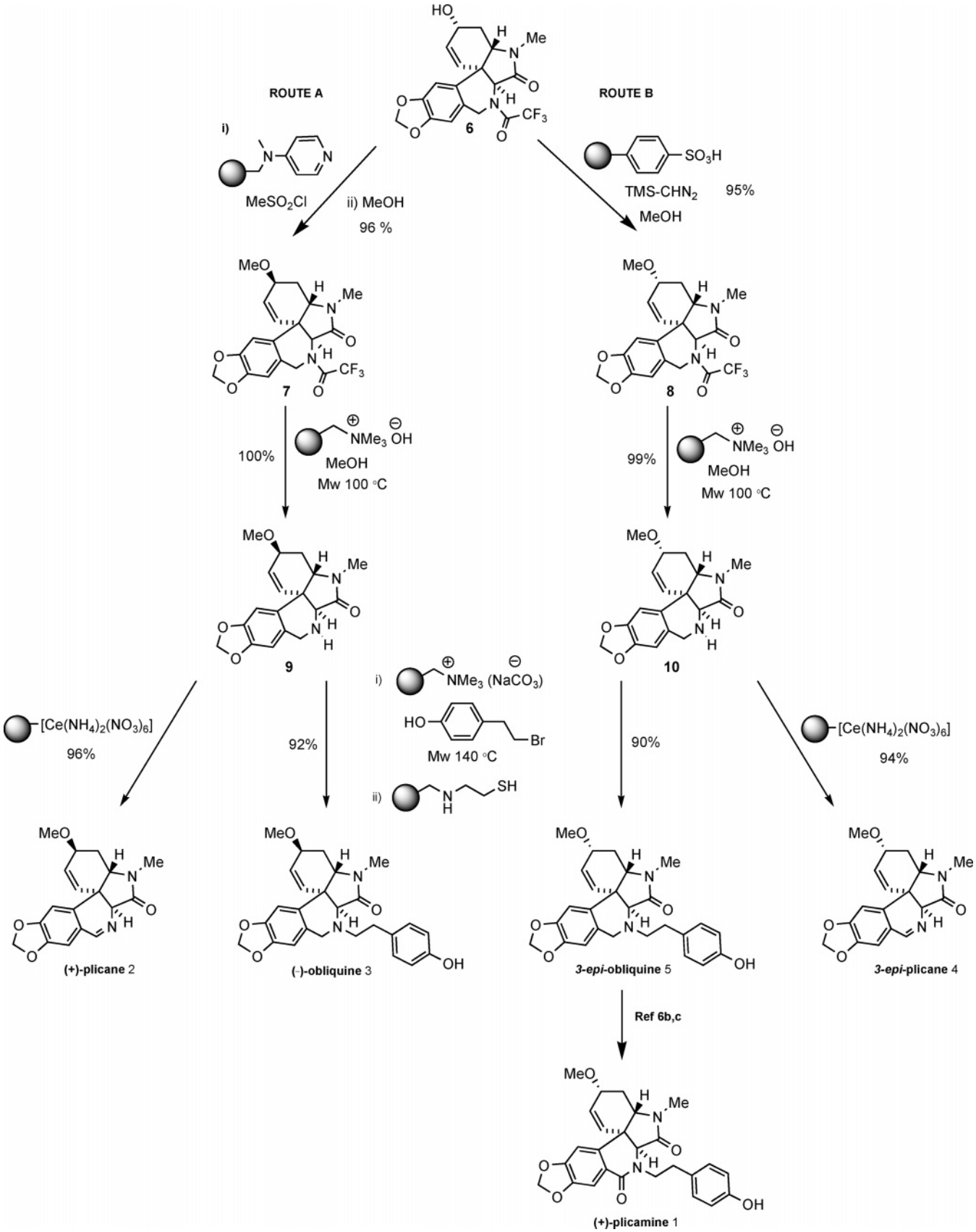
Scheme 1. Synthesis Scheme for the Preparation of Plicamine (1) and Its Derivatives



internal reference (δ_H = 7.26 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ on the same spectrometers, with the central peak of chloroform as the internal reference (δ_C = 77.0 ppm). DEPT 135 was used to aid in the assignment of signals in the ^{13}C NMR spectra.

Plicane (2). Rf 2.530, MS 327.1 (MH^+). $[\alpha]_D$ = 285.9 (c = 0.15 in MeOH); IR(neat), ν_{max}: 3450, 2932, 2850, 1696, 1644, 1609, 1599, 1488, 1386, 1315, 1260, 1186, 1167, 1090, 1028, 987, 837, 820, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (1 H, s, H-8), 6.85 (1 H, s, H-12),

6.78 (1 H, s, H-9), 6.07 (1 H, dd, J = 10.15, 0.85 Hz, H-2), 5.94 (2 H, s, OCH_2O), 5.42 (1 H, d, J = 10.15 Hz, H-1), 4.22 (1 H, br. s, H-6a), 3.73 (1 H, m, H-3), 3.60 (1 H, m, H-4a), 3.39 (3 H, s, OMe), 2.81 (3 H, s, NMe), 2.11 (1 H, m, H-4_B), 1.88 (1 H, m, H-4_A). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (C-6), 158.4 (C-8), 151.0 (C-11), 147.1 (C-10), 131.3 (C-12a), 130.6 (C-1), 129.4 (C-2), 123.1 (C-8_A), 109.2 (C-9), 106.9 (C-12), 101.3 (OCH_2O), 71.5 (C-3), 66.6 (C-6a), 62.3 (C-4a), 56.6 (OMe), 43.6 (C-12b), 30.6 (NMe), 28.4 (C-4). HR-MS Calcd for $C_{18}H_{18}N_2O_4$Na: 349.1164. Found: 349.1170.

Obliquine (3). Rf 2.384, MS 449.1 (MH^+). $[\alpha]_D$ = −137.8 (c = 0.35 in MeOH); IR(neat), ν_{max}: 3311.5, 2970.2, 1716.1, 1670.2, 1513.3, 1488.1, 1456.1, 1400.0, 1233.6, 1158.4, 1108.0, 1036.2, 944.7, 935.7, 933.1 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (2 H, d, J = 8.5 Hz, H-11′), 6.73 (2 H, d, J = 8.5 Hz, H-10′), 6.55 (1 H, s, H-12), 6.46 (1 H, s, H-9), 5.96 (1 H, dd, J = 10.0, 5.2 Hz, H-2), 5.90 (1 H, d, J = 10.0 Hz, H-1), 5.87 (2 H, s, OCH_2O), 3.98 (1 H, d, J = 15.25 Hz, H-8_A), 3.89 (1 H, m, H-3), 3.66 (1 H, dd, J = 11.5 and 4.5 H-4_A), 3.70 (1 H, d, J = 15.25 Hz, H-8_B), 3.66 (1 H, s, H-6_A), 3.48 (3 H, OMe), 3.31 (1 H, m, H-8_A′), 3.27 (1 H, m, H-8_B′), 2.75 (2 H, t, J = 7.9 Hz, H-7′), 2.79 (3 H, s, NMe), 2.26 (1 H, m, H-4_B), 1.89 (1 H, m, H-4_B). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.3 (C-6), 154.8 (C-4′), 147.1, 147.0 (C-10 and C-11), 135.5 (C-1), 132.8 (C-9′), 131.5 (C-12a), 129.5 (C-8a), 129.8 (C-10′), 124.8 (C-2), 115.4 (C-11′), 109.0 (C-9), 107.8 (C-12), 101.9 (OCH_2O), 72.5 (C-3), 66.5 (C-6a), 62.6 (C-4a), 56.8 (C-8′), 56.5 (OMe), 50.6 (C-8), 44.7 (C-12b), 33.9 (C-7′), 32.1 (C-4), 27.8 (NMe). HR-MS Calcd for $C_{26}H_{28}N_2O_5$Na: 471.1896. Found: 471.1892.

***3-Epi*-plicane (4).** Rf 2.426, MS 327.1 (MH^+). $[\alpha]_D$ = 88.7 (c = 0.15 in MeOH); IR(neat), ν_{max}: 3288, 2935, 1675, 1644, 1605, 1525, 1488, 1399, 1234, 1140, 950, 945, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (1 H, s, H-8), 6.81 (1 H, s, H-12), 6.62 (1 H, s, H-9), 6.04 (1 H, dd, J = 10.2, 1.35 Hz, H-2), 5.96 (2 H, s, OCH_2O), 5.50 (1 H, d, J = 10.2 Hz, H-1), 4.39 (1 H, br. s, H-6a), 3.84 (1 H, m, H-3), 3.56 (1 H, dd, J = 12.5, 4.8 Hz, H-4_A), 3.34 (3 H, s, OMe), 2.80 (3 H, s, NMe), 2.13 (1 H, m, H-4_B), 1.86 (1 H, m, H-4_A). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5 (C-6), 159.4 (C-8), 151.9 (C-11), 147.0 (C-10), 131.8 (C-12a), 130.9 (C-1), 130.3 (C-2), 120.9 (C-8a), 109.9 (C-9), 108.3 (C-12), 101.3 (OCH_2O), 73.1 (C-3), 67.1 (C-6a), 62.5 (C-4a), 56.5 (OMe), 40.6 (C-12b), 30.1 (NMe), 28.3 (C-4). X-ray crystal structure obtained of the racemic material registered with the Cambridge Crystallographic Database, under reference CDS 252364.

***3-Epi*-obliquine (5).** Rf 2.721, MS 449.1 (MH^+). $[\alpha]_D$ = 143.6 (c = 0.25 in MeOH); IR(neat), ν_{max}: 3293, 2927, 1669, 1613, 1515, 1483, 1454, 1386, 1234, 1102, 1036, 932, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (2 H, d, J = 8.3 Hz, H-11′), 6.75 (2 H, d, J = 8.3 Hz, H-10′), 6.50 (1 H, d, H−Ar), 6.46 (1 H, d, H−Ar), 5.93 (1 H, d, J = 10.15 Hz, H-1), 5.89 (2 H, s, CH_2O_2), 5.79 (1 H, d, J = 10.15 Hz, H-2), 4.13 (1 H, m, H-3), 3.94 (1 H, m, J = 15.25 Hz, H-8_A), 3.78 (1 H, s, H-6a), 3.67 (1 H, d, J = 15.25 Hz, H-8_B), 3.56 (1 H, dd, J = 12.35, 4.35 Hz, H-4a), 3.45 (3 H, s, OMe), 3.35 (1 H, m, H-8_A′), 3.25 (1 H, m, H-8_B′), 2.76 (5 H, m, H-7′ and NMe), 2.53 (1 H, m, H-4_A), 1.39 (1 H, m, H-4_B); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8 (C-6), 154.7 (C-12′), 146.8 and 146.6 (C-10 and C-11), 133.1 (C-1), 128.3 (C-2), 132.5 (C-9′), 131.8 (C-12a), 129.6 (C-8a), 129.8 (C-10′), 115.4 (C-11′), 107.7 (C-9), 106.3 (C-12), 101.1 (C-15), 74.6 (C-3), 66.4 (C-4a), 64.6 (C-6a), 56.9 (C-8′), 56.2 (OMe), 50.5 (C-8), 44.8 (C-12b), 34.0 and 32.0 (C-4 and C-7′), 27.9 (NMe). HR-MS Calcd for $C_{26}H_{28}N_2O_5$Na: 471.1896. Found: 471.1894.

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Literature Cited

(1) (a) Hodge, P.; Nishikubo, T.; Ober, C. K.; Reichmanis, E.; Sherrington, D. C.; Tomoi, M.; Wohrle, D. Definitions of terms relating to reactions of polymers and to functional polymeric materials (IUPAC Recommendations 2003). *Pure Appl. Chem.* **2004**, *76* (4), 889. (b) Lei, Z.; Denecker, C.; Jegasothy, S.; Sherrington, D. C.; Slater, N. K. H.; Sutherland, A. J. A Facile Route to a Polymer-Supported IBX Reagent. *Tetrahedron Lett.* **2003**, *44*, 1635. (c) van de Water, L. G. A.; Driessen, W. L.; Reedijk, J.; Sherrington, D. C. Metal-Ion Extraction by Immobilised Aza Crown Ethers *Eur. J. Inorg. Chem.* **2002**, *1*, 221. (d) Sherrington. D. C. Polymer-Supported Reagents, Catalysts, and Sorbents: Evolution and Exploitation—A Personalized View. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39* (14), 2364. (e) Wentzel, B. B.; Leinonen, S. M.; Thomson, S.; Sherrington, D. C.; Feiters, M. C.; Nolte, R. J. M. Aerobic Epoxidation of Alkenes Using Polymer-Bound Mukaiyama Catalysts**.** *J. Chem. Soc., Perkin Trans. 1* **2000**, 3428. (f) Sherrington, D. C.; Karjalainen, J. K.; Canali, L.; Deleuze, H.; Hormi, O. E. O. Polymer-Supported Ti(IV) and Mn(III) Asymmetric Alkene Epoxidation Catalysts. *Macromol. Symp.* **2000**, *156*, 125. (g) Deleuze, H.; Schultze, X.; Sherrington, D. C. Reactivity of Some Polymer-Supported Titanium Catalysts in Transesterification and Epoxidation Reactions. *J. Mol. Catal. A* **2000**, *159*, 257. (h) Canali, L.; Cowan, E.; Deleuze, H.; Gibson C. L.; Sherrington, D. C. Polystyrene and Polymethacrylate Resin-Supported Jacobsen's Alkene Epoxidation Catalyst. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2055. (i) Deleuze, H.; Schultze, X.; Sherrington, D. C. Synthesis of Porous Supports Containing *N*-(p-hydroxyphenyl)- or *N*-(3-4-dihydroxybenzyl) maleimide-Anchored Titanates and Application as Catalysts for Transesterification and Epoxidation Reactions. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 2879. (j) van de Water, L. G. A.; ten Hoonte, F.; Driessen, W. L.; Reedijk, J.; Sherrington, D. C. Selective Extraction of Metal Ions by Azathiacrown Ether-Modified Polar Polymers. *Inorg. Chim. Acta* **2000**, *303*, 77. (k) Sherrington. D. C. *Catal. Today* **2000**, *57*, 87. (l) Drake, R.; Sherrington, D. C.; Thomson, S. J. High Surface Area Polystyrene Resin-Supported Pt Catalysts in Room Temperature Solventless Octene Hydrosilylation Using Methyldichlorosilane. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1523. (m) Olason, C.; Sherrington, D. C. *React. Funct. Polym.* **1999**, *42*, 163. (n) Patro, B.; Merrett, M.; Murphy, J. A.; Sherrington, D. C.; Morrison, M. G. J. T. Radical-Polar Crossover Reactions with Polymer-Supported Tetrathiafulvalene. *Tetrahedron Lett.* **1999**, *40*, 7857. (o) Canali, L.; Sherrington, D. C.; Deleuze, H. Synthesis of Resins with Pendently Bound Chiral Manganese-Salen Complexes and Use as Heterogeneous Asymmetric Alkene Epoxidation Catalysts. *React. Funct. Polym.* **1999**, *40*, 155. (p) Leinonen, S.; Sherrington, D. C.; Sneddon, A.; McLoughlin, D.; Corker, J.; Canevali, C.; Morazzoni, F.; Reedijk, J.; Spratt, S. B. D. Molecular Structural and Morphological Characterization of Polymer-Supported Mo(VI) Alkene Epoxidation Catalysts. *J. Catal.* **1999**, *183*, 251. (q) Canali, L.; Cowan, E.; Deleuze, H.; Gibson, C. L.; Sherrington, D. C. Remarkable Matrix Effect in Polymer-Supported Jacobsen's Alkene Epoxidation Catalysts. *Chem. Commun.* **1998**, (23), 2561. (r) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. An Improved Heterogeneous Asymmetric Epoxidation of Homoallylic Alcohols Using Polymer-Supported Ti(IV) Catalysts *Tetrahedron: Asymm.* **1998**, *9*, 21, 3895. (s) Deleuze, H.; Schultze, X.; Sherrington, D. C. Polymer-Supported Titanates as Catalysts for Transesterification Reactions**.** *Polymer* **1998**, *39*, 6109. (t) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C.

An Improved Heterogeneous Asymmetric Epoxidation of Homoallylic Alcohols Using Polymer-Supported Ti(IV) Catalysts. *Tetrahedron: Asymm.* **1998**, *9*, 2019. (u) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. Highly Efficient Heterogeneous Polymer-Supported Sharpless Alkene Epoxidation Catalysts. *Tetrahedron: Asymm.* **1998**, *9*, 1563. (v) Canali, L.; Karjalainen, J. K.; Sherrington, D. C.; Hormi, O. Efficient Polymer-supported Sharpless Alkene Epoxidation Catalyst. *Chem. Commun.* **1997**, (1), 123. (w) Ma, J. B.; Sherrington, D. C. Preparation of Polymer-Supported Palladium(II) Complexes and Use in Anti-Markovnikov Wacker Oxidations of Oct-1-ene to Octanol in *tert*-Butyl Alcohol. *J. Chem. Res. Synop.* **1995**, *4*, 119. (x) Miller, M. M.; Sherrington, D. C. Alkene Epoxidations Catalyzed by Mo(VI) Supported on Imidazole-containing Polymers. 2. Recycling of Polybenzimidazole-Supported Mo(VI) in the Epoxidation of Cyclohexene. *J. Catal.* **1995**, *152*, 377. (y) Tang, H. G.; Sherrington, D. C. Polymer-Supported Pd-(II) Wacker-Type Catalysts. 1.1. Synthesis and Characterization of the Catalyst. *Polymer* **1993**, *34*, 2821. (z) Sherrington, D. C.; Simpson, S. Polymer-Supported Mo Alkene Epoxidation Catalysts *React. Polym*. **1993**, *19*, 13. (aa) Guyot, A.; Hodge, P.; Sherrington, D. C.; Widdecke, H. Recent Studies Aimed at the Development of Polymer-Supported Reactants with Improved Accessibility and Capacity. *React. Polym.* **1992**, *16*, 233. (ab) Sherrington, D. C. Polymer-Supported Systems—Towards Clean Chemistry. *Chem. Ind*. **1991**, *1*, 15. (ac) Hodge, P.; Sherrington, D. C. 2nd International Meeting on Polymer-Supported Reactions in Organic Chemistry—Introduction. *Br. Polym. J.* **1984**, *16*, 163. (ad) Akelah, A.; Sherrington, D. C. Recent Developments in the Application of Functionalized Polymers in Organic Synthesis. *Polymer* **1983**, *24*, 1369. (ae) McKenzie, W. M.; Sherrington, D. C. Polymer-Supported Phosphines—Reactivity of Pendant and Cross-Link Groups. *J. Polym. Sci., Part A: Polym. Chem*. **1982**, *20*, 431. (af) Akelah, A.; Sherrington, D. C. Application of Functionalized Polymers in Organic-Synthesis. *Chem. Rev.* **1981**, *81*, 557.

(2) For a recent review, see: Jin, Z.; Li, Z.; Huang, R. Muscarine, Imidazole, Oxazole, Thiazole, Amaryllidaceae and *Sceletium* Alkaloids. *Nat. Prod. Rep.* **2002**, *19,* 454.

(3) For reviews on multistep applications, see: (a) Baxendale, I. R.; Storer, R. I.; Ley, S. V. Supported Reagents and Scavengers in Multi-Step Organic Synthesis. In *Polymeric Materials in Organic Synthesis and Catalysis*; Buchmeiser, M. R., Ed. Wiley−VCH: Berlin, 2003, Chapter 2, pp 53−136. (ISBN 3-527-3063-7.) (b) Ley, S. V.; Baxendale, I. R. *Chem. Rec.* **2002**, *2*, 377. (c) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discovery* **2002**, 573. (d) Ley, S. V.; Baxendale, I. R. The Development and Application of Supported Reagents for Multistep Organic Synthesis. In *Supported Catalysts and Their Applications*; Sherrington, D. C., Kybett, A. P., Eds.; The Royal Society of Chemistry, 2001; Chapter 2, pp 9−18. (IBSN 0−85404−880−4.) (e) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. Multistep Organic Synthesis Using Solid-Supported Reagents and Scavengers: A New Paradigm in Chemical Library Generation. *J. Chem. Soc., Perkin Trans 1* **2000**, 3815. (f) Hall, B.; Haunert, F.; Scott, J.; Bolli, M.; Habermann, J.; Hinzen, B.; Ley, S. V.; Gervois, A-.G. Preparation of Compounds Using Polymer Supported Reagents, Patent WO 9958475, 1999.

(4) For general reviews, see: (a) Bhattacharyya, S. New Developments in Polymer-Supported Reagents, Scavengers and Catalysts for Organic Synthesis. *Curr. Opin. Drug Discovery Dev*. **2004**, *7*, 752. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. Functionalized Polymers—Emerging Versatile Tools for Solution-Phase Chemistry and Automated Parallel Synthesis. *Angew. Chem., Int. Ed.* **2001**, *40*, 650. (c) Clapham, B.; Reger, T. S.; Janda, K. D. Polymer-Supported Catalysis in Synthetic Organic Chemistry. *Tetrahedron* **2001**, *57*, 4637. (d) Bhattacharyya, S. Polymer-Assisted Solution-Phase Organic Synthesis: Advances in Multistep Synthetic Applications. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2001**, *40*, 878. (e) Thompson, L. A. Recent Applications of Polymer-Supported Reagents and Scavengers in Combinatorial, Parallel, or Multistep Synthesis. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324. (f) Kobayashi, S. Immobilized Catalysts in Combinatorial Chemistry. *Curr. Opin. Chem. Biol.* **2000**, *4*, 338. (g) Bhattacharyya, S. Polymer-Supported Reagents and Catalysts: Recent Advances in Synthetic Applications. *Comb. Chem. High Throughput Screening* **2000**, *3*, 3998. (h) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, *8*, 1035. (i) Booth R. J.; Hodges, J. C. Solid-Supported Reagent Strategies for Rapid Purification of Combinatorial Synthesis Products. *Acc. Chem. Res.* **1999**, *32*, 18. (j) Parlow, J. J.; Devraj, R. V.; South, M. S. Solution-Phase Chemical Library Synthesis Using Polymer-Assisted Purification Techniques. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320. (k) Drewry, D. H.; Coe, D. M.; Poon, S. Solid-Supported Reagents in Organic Synthesis. *Med. Res. Rev.* **1999**, *19*, 97. (l) Booth, R. J.; Hodges, J. C. Polymer-Supported Quenching Reagents for Parallel Purification. *J. Am. Chem. Soc.* **1997**, *19*, 44882. (m) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. Functionalised Polymers: Recent Developments and New Applications in Synthetic Organic Chemistry. *Synthesis* **1997**, 1217. (n) Kaldor, S. W.; Siegel, M. G.; Dressman, B. A.; Hahn, P. J. Use of Solid Supported Nucleophiles and Electrophiles for the Purification of Non-peptide Small Molecule Libraries. *Tetrahedron Lett.* **1996**, *37*, 7193. (o) Chakrabarti, A.; Sharma, M. M. *React. Polym.* **1993**, *20*, 1. (p) Sussman, S. Catalysis by Acid-Regenerated Cation Exchangers. *Ind. Eng. Chem.* **1946**, *38*, 1228.

(5) For specific examples from our laboratory, see: (a) Storer, R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. Multi-Step Application of Immobilized Reagents and Scavengers: A Total Synthesis of Epothilone C. *Chem.—Eur. J*. **2004**, *10*, 2529. (b) Baxendale, I. R.; Davidson, T. D.; Ley, S. V.; Perni, R. H. Enantioselective Synthesis of the Tetrahydrobenzylisoquinoline Alkaloid (−)-Norarmepavine Using Polymer-Supported Reagents. *Heterocycles* **2003***, 60*, 2707. (c) Storer, R. I.; Takemoto, T.; Jackson, P. S.; Ley, S. V. A Total Synthesis of Epothilones Using Solid-Supported Reagents and Scavengers. *Angew. Chem., Int. Ed*. **2003**, *42*, 2521. (d) Bream, R. N.; Ley, S. V.; Procopiou, P. A. Synthesis of the β2 Agonist (*R*)-Salmeterol Using a Sequence of Supported Reagents and Scavenging Agents. *Org. Lett*. **2002**, *4*, 3793. (e) Baxendale, I. R.; Brusotti, G.; Matsuoka, M.; Ley, S. V. Synthesis of Nornicotine, Nicotine and Other Functionalised Derivatives Using Solid-Supported Reagents and Scavengers. *J. Chem. Soc., Perkin Trans. 1* **2002**, 143. (f) Ley, S. V.; Taylor, S. J. A Polymer-Supported [1,3,2]Oxazaphospholidine for the Conversion of Isothiocyanates to Isocyanides and Their Subsequent Use in an Ugi Reaction. *Biorg. Med. Chem. Lett*. **2002**, *10*, 1813. (g) Ley, S. V.; Massi, A. Parallel Solution-Phase Syntheses of Functionalised Bicyclo-[2.2.2]octanes: Generation of a Library Using Orchestrated Multistep Sequences of Polymer-Supported Reagents and Sequesterants. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3645. (h) Baxendale, I. R.; Ley, S. V. Polymer-Supported Reagents for Multi-Step Organic Synthesis: Application to the Synthesis of Sildenafil. *Biorg. Med. Chem. Lett*. **2000**, *10*, 1983. (i) Habermann, J.; Ley, S. V.; Scott, J. S. Synthesis of the Potent Analgesic Compound (±)-Epibatidine Using an Orchestrated Multistep Sequence of Polymer Supported Reagents. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253. (j) Caldarelli, M.; Habermann, J.; Ley, S. V. Clean Five-Step Synthesis of an Array of 1,2,3,4-Tetra-substituted Pyrroles Using Polymer-Supported Reagents. *J. Chem. Soc., Perkin Trans. 1* **1999**, 107. (k) Habermann, J.; Ley, S. V.; Scicinski, J. J.; Scott, J. S.; Smits, R.; Thomas, A. W. Clean Synthesis of α-Bromo Ketones and Their Utilisation in the Synthesis of 2-Alkoxy-2,3-dihydro-2-aryl-1,4-benzodioxanes, 2-Amino-4-aryl-1,3-thiazoles and Piperidino-2-amino-1,3-thiazoles Using Polymer-Supported Reagents. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2425. (l) Habermann, J.; Ley, S. V.; Smits, R. Three-Step Synthesis of an Array of Substituted Benzofurans Using Polymer-Supported Reagents. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2421. (m) Calderalli, M.; Habermann, J.; Ley, S. V. Synthesis of an Array of Potential Matrix Matalloproteinase Inhibitors Using a Sequence of Polymer-Supported Reagents. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2049. (n) Hinzen, B.; Lenz, R.; Ley, S. V. Polymer Supported Perruthenate (PSP): Clean Oxidation of Primary Alcohols to Carbonyl Compounds Using Oxygen as Cooxidant *Synthesis* **1998**, 977. (o) Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois A.-G.; Hall, B. J. Use of Polymer Supported Reagents for Clean *Multistep* Organic Synthesis: Preparation of Amines and Amine Derivatives from Alcohols for Use in Compound Library Generation. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239. (p) Haunert, F.; Bolli, M. H.; Hinzen, B.; Ley, S. V. Clean Three-Step Synthesis of 4,5-Dihydro-1*H*-pyrazoles Starting from Alcohols Using Polymer Supported Reagents. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2235. (q) Habermann, J.; Ley, S. V.; Scott, J. S. Clean Six-Step Synthesis of a Piperidinothiomorpholine Library Using Polymer-Supported Reagents. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3127. (r) Hinzen, B.; Ley, S. V. Polymer Supported Perruthenate (PSP): A New Oxidant for Clean Organic Synthesis. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1907. (s) Lenz, R.; Ley, S. V. Tetra-*n*-propylammonium perruthenate

(TPAP)-Catalysed Oxidations of Alcohols Using Molecular Oxygen as a Co-oxidant. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3291.

(6) (a) Ley, S. V.; Schucht, O.; Thomas, A. W.; Murray, P. J. Synthesis of the Alkaloids (±)-Oxomaritidine and (±)-Epimaritidine Using an Orchestrated Multistep Sequence of Polymer Supported Reagents. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1251. (b) Baxendale, I. R.; Ley, S. V.; Piutti, C. Total Synthesis of the Amaryllidaceae Alkaloid (+)-Plicamine and Its Unnatural Enantiomer by Using Solid-Supported Reagents and Scavengers in a Multistep Sequence of Reactions. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194. (c) Baxendale, I. R.; Ley, S. V.; Nesi, M.; Piutti, C. Total Synthesis of the Amaryllidaceae Alkaloid (+)-Plicamine Using Solid-Supported Reagents. *Tetrahedron* **2002**, *58*, 6285.

(7) Ünver, N.; Gözler, T.; Walch, N.; Gözler, B.; Hesse, M. Two Novel Dinitrogenous Alkaloids from *Galanthus plicatus* subsp. Byzantinus (Amaryllidaceae). *Phytochemistry* **1999**, *50*, 1255.

(8) Brickell, C. D. In *Flora of Turkey and the East Aegean Islands*; Davis, P. H., Ed.; Edinburgh University Press: Edinburgh, U.K., 1984; Vol. 8, p 367.

(9) Ünver, N.; Noyan, S.; Gözler, B.; Gözler, T.; Werner, C.; Hesse, M. Four New Amaryllidaceae Alkaloids from *Galanthus gracilis* and *Galanthus plicatus* subsp Byzantinus. *Heterocycles* **2001**, *55*, 641.

(10) DuPlessis, N.; Duncan, G. D. In *Bulbous Plants of Southern Africa*; Tafelberg Publishers, Ltd.: Cape Town, South Africa, 1989.

(11) Brine, N. D.; Campbell, W. E.; Bastida, J.; Herrera, M. R.; Viladomat, F.; Codina, C.; Smith, P. J. A Dinitrogenous Alkaloid from *Cyrtanthus obliquus*. *Phytochemistry* **2002**, *61*, 443.

(12) (a) Loupy, A., Ed. *Microwaves in Organic Synthesis*; Wiley−VCH: Weinheim, Germany, 2003. (b) Baxendale, I. R.; Lee, A.-L.; Ley, S. V. Integrating Microwave-Assisted Synthesis and Solid-Supported Reagents. In *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidström, P., Eds.; Blackwell Publishing: Oxford, U.K., 2005; Chapter 6, p 133.

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