COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Synthesis and application of chiral bisphosphines through lithiation–conjugate addition tandem cyclization of chiral α,β,ψ,ω-unsaturated bisphosphine oxide

Yasuo Nagaoka, Hideki Inoue, Nawal El-Koussi† and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: tomioka@pharm.kyoto-u.ac.jp

Received (in Cambridge, UK) 16th October 2001, Accepted 28th November 2001
First published as an Advance Article on the web 7th January 2002

Upon treatment with lithium diisopropylamide achiral and chiral α,β,ψ,ω-unsaturated bisphosphine oxides underwent lithiation–conjugate addition tandem cyclization to afford the corresponding endo-α,β-unsaturated cyclic bisphosphine oxides; sequential stereoselective reduction of the cyclized bisphosphine oxide gave the corresponding *trans*- and *cis*-bisphosphines that were successfully applicable in a catalytic asymmetric hydrogenation as chiral bisphosphine ligands.

As part of our studies aimed at a synthetic application of lithium phosphonates,[1] we have developed an organolithium-initiated conjugate addition–Michael tandem cyclization of α,β,ψ,ω-unsaturated bisphosphonates **3** giving the corresponding carbocycles bearing two phosphonate moieties.[2] If selective deprotonation of an α-vinylic proton of **3** is possible, intramolecular Michael addition of the resulting α-vinyl anion **4** produces endo-α,β-unsaturated cyclic bisphosphonates and bisphosphine oxides **5** (Fig. 1). In contrast to the established double Michael reaction of α,β,ψ,ω-unsaturated biscarboxylates for an efficient way to construct carbocycles,[3] such a lithiation–cyclization sequence is a unique feature of the unsaturated bisphosphonates or bisphosphine oxides **3**. Since phosphonates are isosteric analogues of natural phosphates, nucleotides, amino acids and so on,[4,5] and they are also versatile synthetic precursors of olefins[6] as well as chiral phosphine ligands,[7] the synthetic methodology for **5** is desirable to be developed. We describe herein the facile and selective synthesis of **5** through lithiation–Michael cyclization of **3** with lithium diisopropylamide.

† Visiting scientist from Faculty of Pharmacy, Assiut University, Egypt.

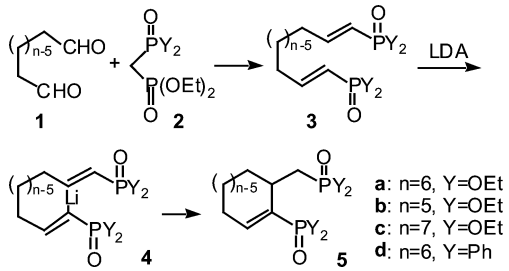

Fig. 1 Synthesis and cyclization of **3**.

Asymmetric cyclization was also carried out using a chiral α,β,ψ,ω-unsaturated phosphine oxide **7**.

Unsaturated bisphosphonates and phosphine oxides **3** were readily prepared by the Horner–Wadsworth–Emmons reaction of methylenebisphosphonates or diethyl(diphenylphosphoryl)methylphosphonate **2**[8] with the corresponding α,ψ-dialdehydes **1**[9] (Fig. 1). Reaction of **3a** (Y = OEt, *n* = 6) with 1.3 equivalents of LDA in THF at −78 °C for 10 min afforded the corresponding six-membered bisphosphonate **5a** (Y = OEt, *n* = 6) as a sole product in 82% yield. No products derived from a conjugate addition of LDA to **1a** were observed.[2] Likewise, the five-membered bisphosphonate **5b** (Y = OEt, *n* = 5) was obtained in 75% yield by treating **3b** with LDA for 20 min at −78 °C. The seven-membered bisphosphonate **5c** (Y = OEt, *n* = 7) was not a suitable target and was obtained in 16% yield by the treatment of **3c** at −20 °C for 10 min.[10] The cyclization of bisphosphine oxides **3d** (Y = Ph, *n* = 6) with LDA in THF was also examined and was found to be quite difficult due to its extremely low solubility in a variety of solvents.

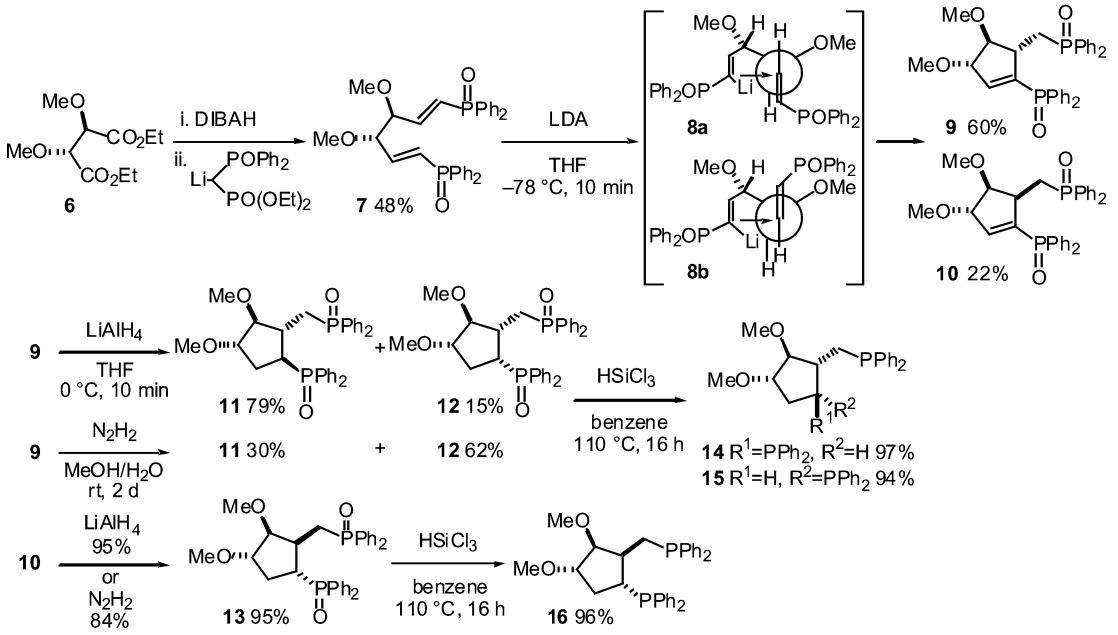

Fig. 2 Tandem cyclization of **7** and conversion to biphosphates **14**–**16**.

DOI: 10.1039/b109269c

We extended the lithiation–Michael cyclization of **3** to an asymmetric reaction of a chiral α,β,ψ,ω-unsaturated bisphosphine oxide **7** prepared from L-tartaric acid (Fig. 2). DIBAL-H reduction of the dimethyl ether of ethyl tartrate **6**[11] followed by Horner–Wadsworth–Emmons reaction of diethyl(diphenylphosphoryl)methylphosphonate **2** (Y = Ph) gave an unsaturated bisphosphine oxide **7** in 48% overall yield. Reaction of **7** with LDA in THF at −78 °C for 10 min afforded tandem cyclization products (−)-**9** in 60% yield and (−)-**10** in 22% yield. The newly created asymmetric centers of **9** and **10** were assigned by NMR analysis, especially NOE measurement. Selective production of **9** as a major carbocycle was ascribable to the favorable cyclization shown in **8a**, where the vinyl anion attacks an olefin carbon from the direction opposite to the adjacent methoxy group. The unsaturated phosphine moiety in **8a** takes a more stable conformation than that in **8b** that produces **10**. Lithium aluminium hydride treatment of **9** in THF at 0 °C underwent 1,4-reduction to afford *trans*-**11** and *cis*-**12** in 79% and 15% yields, respectively. Diimide reduction of **9** in aqueous methanol, on the contrary, gave *cis*-**12** as a major isomer in 62% yield together with *trans*-**11** in 30% yield. Both reduction methods were applied to **10** and, however, gave *trans*-**13** as a sole product without formation of *cis* product, probably due to severe steric repulsion by three contiguous *cis*-groups on the five-membered ring. These phosphine oxides were readily converted to the requisite bisphosphines by deoxygenation with trichlorosilane in benzene at 110 °C in nearly quantitative yields.

Chiral bisphosphines prepared as above were applicable into catalytic asymmetric reactions. For example, catalytic asymmetric hydrogenation of **17** under 5 atmospheres of hydrogen gas with 0.1 mol% of **15** and rhodium(NBD)$_2$ perchlorate[12] in methanol at 50 °C for 24 h afforded quantitatively *N*-acetyl phenylalanine **18** in 90% ee (Fig. 3).[13]

In summary, we have developed a lithiation–cyclization procedure of readily available chiral and achiral α,β,ψ,ω-unsaturated bisphosphine oxides and bisphosphonates for the conventional synthesis of chiral bisphosphines, which were useful as chiral ligands for catalytic asymmetric reactions. Application of the bisphosphines obtained here into the chiral ligands for asymmetric reactions is the focus of our current study.

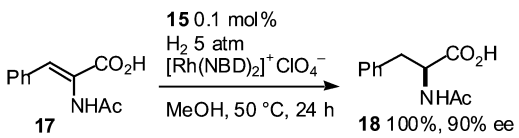

Fig. 3 Catalytic asymmetric hydrogenation with **15**.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan. N. E.-K. acknowledges financial support from the Ministry of Higher Education of Egypt.

Notes and references

1 (*a*) Y. Nagaoka and K. Tomioka, *J. Org. Chem.*, 1998, **63**, 6428; (*b*) M. Mizuno, K. Fujii and K. Tomioka, *Angew. Chem., Int. Ed.*, 1998, **37**, 515.
2 Y. Nagaoka and K. Tomioka, *Org. Lett.*, 1999, **1**, 1467.
3 For the double Michael cyclization of unsaturated carbonyl compounds, see: (*a*) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, London, 1992; (*b*) R. A. Bunce, *Tetrahedron*, 1995, **51**, 13103; (*c*) T. Uyehara, N. Shida and Y. Yamamoto, *J. Org. Chem.*, 1992, **57**, 3139.
4 For reviews on alkylphosphonates, see: (*a*) R. L. Hilderbrand, *The Role of Phosphonates in Living Systems*, CRC Press, Boca Raton, FL, 1983; (*b*) R. Engel, in *Handbook of Organophosphorus Chemistry*, ed. R. Engel, Marcel Dekker, New York, 1992, ch. 11; (*c*) R. Engel, *Chem. Rev.*, 1977, **77**, 349; (*d*) G. A. Rodan, *Annu. Rev. Pharmacol. Toxicol.*, 1998, **38**, 375.
5 Bisphosphonates were used as receptor molecules for the anomer-selective recognition of amino sugars. T. Schrader, *J. Am. Chem. Soc.*, 1998, **120**, 11816.
6 S. E. Kelly, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, 1991.
7 (*a*) K. Tomioka, *Synthesis*, 1990, 541; (*b*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, Inc., New York, 1994; (*c*) F. Lagasse and H. B. Kagan, *Chem. Pharm. Bull.*, 2000, **48**, 315.
8 Methylenebisphosphonate **2** (Y = OEt) is commercially available. Diethyl(diphenylphosphoryl)methylphosphonate **2** (Y = Ph) was prepared by the lithiation of methyl(diphenyl)phosphine oxide with LDA and then treatment with dichlorophosphonate, see: M.-P. Teulade, P. Savignac, E. E. Aboujaoude, S. Lietge and N. Collignon, *J. Organomet. Chem.*, 1986, **304**, 283.
9 J. Fakstorp, D. Raleigh and L. E. Schniepp, *J. Am. Chem. Soc.*, 1950, **72**, 869.
10 A large amount of mixture of polymeric products was obtained.
11 D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H.-A. Oei and M. Schmidt, *Helv. Chim. Acta.*, 1977, **60**, 301.
12 (*a*) K. Inoguchi and K. Achiwa, *Synlett*, 1991, 49; (*b*) T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa and K. Yamaguchi, *J. Am. Chem. Soc.*, 1998, **120**, 1635.
13 Hydrogenation with *trans*-**14** and **16** gave quantitatively **18** in 22% ee and 21% ee.