ORGANIC LETTERS

2009
Vol. 11, No. 13
2912−2915

Desymmetrization of Hydrazinocyclohexadienes: A New Approach for the Synthesis of Polyhydroxylated Aminocyclohexanes

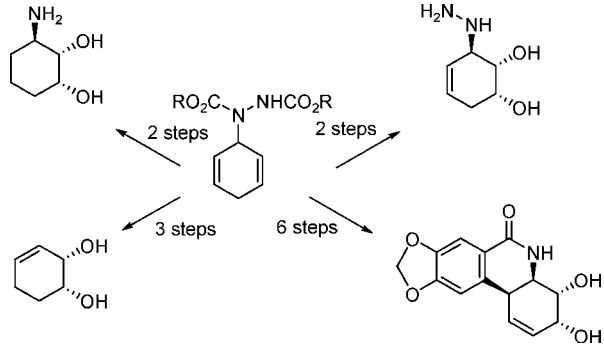
Gauthier Errasti,[†] Cyrille Koundé,[†] Olivier Mirguet,[‡] Thomas Lecourt,[†] and Laurent Micouin*,[†]

Laboratoire de Chimie Thérapeutique, UMR 8638 associée au CNRS et à l'Université Paris Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, 4 av de l'Observatoire, 75270 Paris cedex 06, France, and CEDD−Laboratoire GlaxoSmithKline, 25−27 avenue du Québec, 91951 Les Ulis, France

laurent.micouin@parisdescartes.fr

Received April 10, 2009

ABSTRACT



Hydrazinocyclohexadienes, easily prepared by an ene-reaction between commercially available azodicarboxylate reagents and cyclohexadiene, are interesting substrates for desymmetrization reactions. Under Sharpless asymmetric dihydroxylation conditions, they can lead efficiently to several chiral building blocks as well as advanced precursors of biologically active compounds.

Desymmetrization of cyclohexa-1,4-dienes is among the most efficient strategies to prepare in a few synthetic transformations a large variety of polyfunctional cyclohexanes in a stereoselective manner.[1] The synthetic potential of this approach is due in part to the great number of asymmetric transformations available to convert cyclohexadienes into valuable intermediates and also to the availability of the racemic starting material. These compounds are typically prepared by a Birch reduction or reductive alkylation of aromatic compounds, leading to the symmetrical cyclohexa-1,4-dienes bearing a tertiary or quaternary prochiral center.[2] An elegant variant of this strategy based on metalated cyclohexadienes has also been recently proposed by Studer and co-workers.[3]

[†] University Paris Descartes, CNRS.
[‡] GlaxoSmithKline.

(1) (a) Abd Rahman, N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369. (b) Studer, A.; Schleth, F. *Synlett* **2005**, 3033.

(2) (a) Angelaud, R.; Landais, Y. *J. Org. Chem.* **1996**, *61*, 5202. (b) Angelaud, R.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, *64*, 9613. (c) Landais, Y.; Zekri, E. *Eur. J. Org. Chem.* **2002**, 4037. (d) Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.* **2005**, *7*, 4557. (e) Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755. (f) Crich, D.; Krishnamurthy, V. *Tetrahedron* **2006**, *62*, 6830. (g) Beniazza, R.; Dunet, J.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2007**, *9*, 3913. (h) Butters, M.; Elliot, M. C.; Hill-Cousins, J.; Paine, J. S.; Walker, J. K. E. *Org. Lett.* **2007**, *9*, 3635.

10.1021/ol900779v CCC: $40.75
Published on Web 05/26/2009

In our ongoing work on the use of *meso* hydrazines for the stereoselective synthesis of polyfunctional amino or hydrazinocyclopentanes,[4] we were interested to access the corresponding cyclohexanic homologues via a similar strategy. In this context, hydrazinocyclohexadienes **1** seemed to be attractive substrates (Figure 1). These compounds are

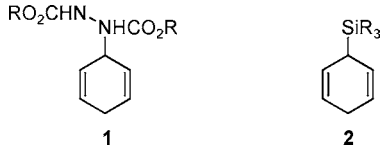


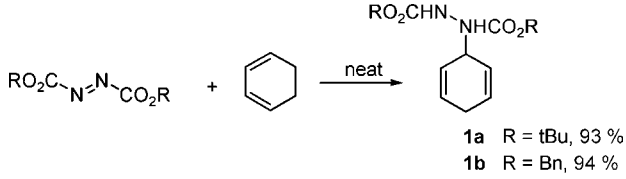
Figure 1. Hydrazino- or silylated dienes for desymmetrization studies.

indeed readily prepared on multigram quantities by a nearly quantitative solvent-free ene-reaction between cyclohexadiene and commercial azodicarboxylates, as first reported in the early 1960s.[5] They can be considered as nitrogenated analogues of silylated dienes **2**, known to be excellent precursors for the synthesis of aminocyclitols since the now classical pioneering work of Landais and co-workers in this field.

Herein, we outline the desymmetrization of substrates **1** and their subsequent transformations as a new entry to the frequently encountered aminocyclohexanediol framework.[6]

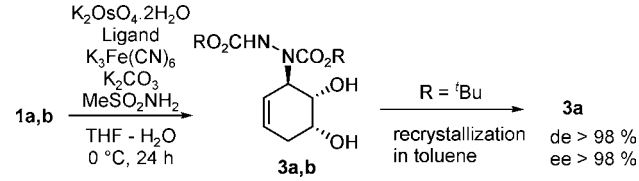
Compounds **1a**,**b** were prepared as previously reported and were obtained as stable solids on a large (20−30 g) scale (Scheme 1).

Scheme 1. Solvent-Free Synthesis of Dienes **1a,b**



Asymmetric dihydroxylation of these substrates was then investigated.[7] Despite structural analogy between compounds **1** and **2**, the stability of hydrazines **1** under oxidative conditions was unknown.[8] We were therefore pleased to see that dihydroxylated compounds **3a,b** could be obtained under Sharpless biphasic conditions, without significant aromatization or oxidative cleavage. The dihydroxylation reaction proved to be fully diastereoselective, leading to the *anti* diastereomers (Table 1). Enantiomeric excesses were in the

Table 1. Asymmetric Dihydroxylation of Dienes **1a,b**



		R = *t*Bu, **3a**		R = Bn, **3b**	
entry	ligand	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[c]
1	$(DHQ)_2AQN$	58	35	44	35
2	$(DHQD)_2AQN$	62	45	52	50
3	$(DHQ)_2PYR$	32	26	40	24
4	$(DHQD)_2PYR$	45	14	37	16
5	$(DHQ)_2PHAL$	40	41	44	41
6	$(DHQD)_2PHAL$	69[d]	55[d]	43	47

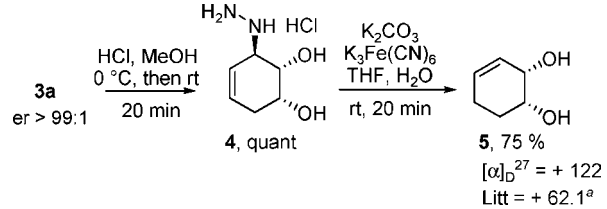
[a] Isolated yield. [b] Determined by chiral HPCL analysis. [c] Determined by chiral HPCL analysis hydrogenolysis and acetylation. [d] Reaction conducted on a 20 g scale.

range of those obtained from silylated dienes **2**, the best results beeing obtained with $(DHQD)_2PHAL$ ligand and compound **1a** (entry 6).

Interestingly, enantiomerically pure hydrazinodiol **3a** can be obtained at this stage by recrystallization in toluene, thus preventing the problems of enantiomeric purity encountered in the silylated series. As the desymmetrization step can be conducted on a large scale (20 g), this new route enables the preparation of a large amount of enantiomerically pure compound **3a**.

The absolute configuration of compound **3a** was established by chemical correlation (Scheme 2). Thus, compound

Scheme 2. Determination of Absolute Configuration of **3a** by Chemical Correlation



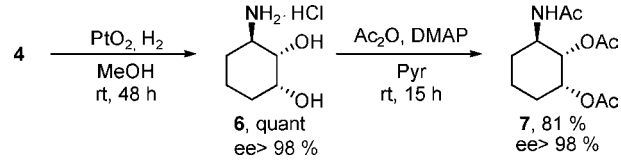
[a] Determined for enantiomerically enriched (33% ee) material. See ref 11.

3a was first quantitatively deprotected under acidic conditions, and the resulting hydrochloride was submitted to an oxidative treatment delivering the corresponding diol **5** by

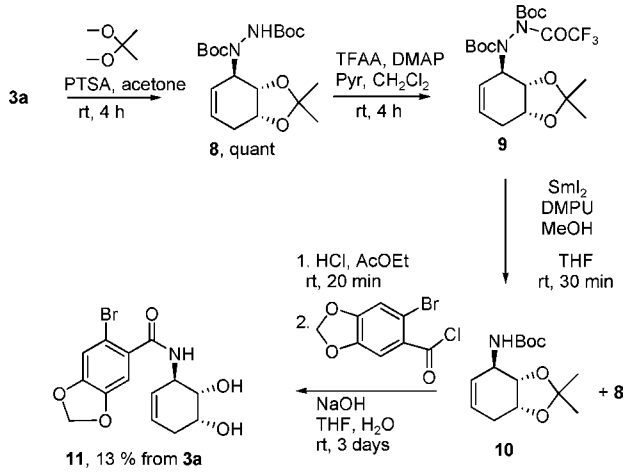
(3) (a) Schleth, F.; Studer, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 313. (b) Schleth, F.; Vogler, T.; Harms, K.; Studer, A. *Chem.—Eur. J.* **2004**, *10*, 4171. (c) Maji, M. S.; Fröhlich, R.; Studer, A. *Org. Lett.* **2008**, *10*, 1847.

(4) (a) Perez Luna, A.; Ceschi, M.-A.; Bonin, M.; Micouin, L.; Husson, H.-P.; Gougeon, S.; Estenne-Bouhtou, G.; Marabout, B.; Sevrin, M.; George, P. *J. Org. Chem.* **2002**, *67*, 3522. (b) Perez Luna, A.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Am. Chem. Soc.* **2002**, *124*, 12098. (c) Perez Luna, A.; Cesario, M.; Bonin, M.; Micouin, L. *Org. Lett.* **2003**, *5*, 4771. (d) Bunlaksananusorn, T.; Perez Luna, A.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240. (e) Alexakis, A.; Polet, D.; Bournaud, C.; Bonin, M.; Micouin, L. *Tetrahedron: Asymmetry.* **2005**, *16*, 3672. (f) Bournaud, C.; Lecourt, T.; Micouin, L.; Méliet, C.; Agbossou-Niedercorn, F. *Eur. J. Org. Chem.* **2008**, 2298. (g) Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, *8*, 3581.

Scheme 3. Synthesis of Aminocyclohexanediols **6** and **7**

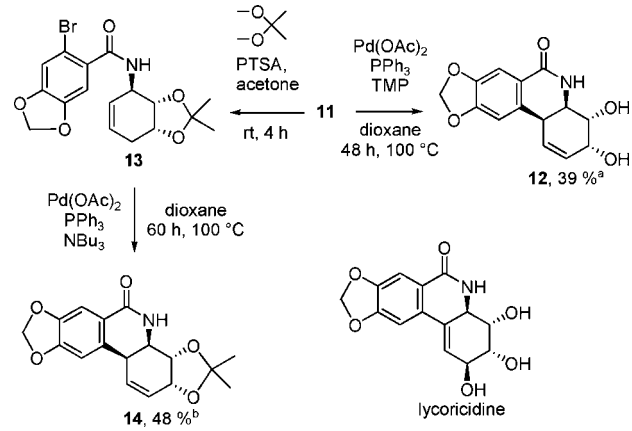


Scheme 4. Synthesis of Alkaloids Precursors



retro-ene reaction after a simple biphasic extraction in 75% overall yield. Although retro-ene reactions involving allylic hydrazines are generally triggered by a base-catalyzed elimination of substituted benzenesulfinic acid,[9] we found that generating the allylic azo intermediate under biphasic oxidative conditions was even more straightforward.[10] This

Scheme 5. Acces to Poly-oxygenated Phenanthridone Skeleton



[a] 78% based on unreacted recovered starting material. [b] 81% based on unreacted recovered starting material.

four-step enantioselective synthesis of cyclohexene diol **5** from cyclohexadiene compares favorably with any other routes reported for the preparation of this useful synthetic intermediate. The determination of the absolute configuration of compound **3a** confirmed that dienes **1** and **2** behave similarly under Sharpless asymmetric dihydroxylation conditions, the same absolute and relative configuration being obtained with the same ligands.

Several other simple synthetic transformations can be carried out on compound **3a**. Diastereo- and enantiomerically pure aminocyclohexanediol **6** was for example obtained by a Pt-catalyzed hydrogenolysis. This compound was peracetylated, enabling the confirmation of its *anti* relative configuration by NMR analysis.

Finally, a new route to the skeleton of oxygenated alkaloids from Amaryllidaceae was explored.[12] For this purpose, a selective hydrazine cleavage was needed, without any double reduction or isomerization. Although numerous reductive cleavages of hydrazines have been reported, this step proved to be particularly difficult. We found, after extensive investigations, that reductive TFA-promoted cleavage by SmI_2 was the most appropriate method to achieve this goal.[13] This reaction was systematically accompanied by the solvolysis of the trifluoroacetamide moiety of tetrasubstituted hydrazine **9**, which proved to be rather unstable, leading back

(5) (a) Gillis, B. T.; Beck, P. E. *J. Org. Chem.* **1962**, *27*, 1947. (b) Franzus, B.; Surridge, J. H. *J. Org. Chem.* **1962**, *27*, 1951. (c) Franzus, B. *J. Org. Chem.* **1963**, *28*, 2954. For a review on ene-reactions, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1969**, *8*, 556.

(6) For selected recent examples of diastereoselective syntheses of the aminocyclohexanediol motif, see:(a) Aciro, C.; Davies, S. G.; Kurosawa, W.; Roberts, P. M.; Russel, A. J.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1333. (b) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russel, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762. (c) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russel, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751. (d) Davies, S. G.; Long, M. C.; Smith, A. D. *Chem. Commun.* **2005**, *36*, 4536.

(7) For selected examples of diastereoselective dihydroxylation of allylic cyclohexanic amines, see: (a) Huang, J.; Bergmeier, S. C. *Tetrahedron* **2008**, *64*, 6434. (b) Verhelst, S. H. L.; Wennekes, T.; van der Marel, G. A.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron* **2004**, *60*, 2813. (c) Ko, H.; Kim, E.; Park, J. E.; Kim, D.; Kim, S. *J. Org. Chem.* **2004**, *69*, 112. (d) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombde, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946. (e) Jana, C. K.; Studer, A. *Chem.—Eur. J.* **2008**, *14*, 6326.

(8) As "proaromatic substrates", cyclohexadienes **1** could be expected to easily aromatize under metal-catalyzed oxidative conditions, with or without C−N bound cleavage. The use of biphasic conditions might prevent this problem. For a review on this reactivity, see :Walton, J. C.; Studer, A. *Acc. Chem. Res.* **2005**, *38*, 794.

(9) (a) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572. (b) Movassaghi, M.; Ahmad, O. K. *J. Org. Chem.* **2007**, *72*, 1838, and references therein.

(10) For an early example of retro-ene triggered by oxidation of allylic hydrazines, see: Baldwin, J. E.; Brown, J. E.; Höfle, G. *J. Am. Chem. Soc.* **1971**, *93*, 788.

(11) (a) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *J. Org. Chem.* **1994**, *59*, 54. All configurational assignments are reversed in this publication; see erratum: Takano, S.; Yoshimitsu, T.; Ogasawara, K. *J. Org. Chem.* **1995**, *60*, 1478. (b) Wang, Z.-M.; Kakiuchi, K.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 6895.

(12) Review: Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, *108*, 1982.

(13) (a) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637. (b) Fernandez, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461. (c) Friestad, G. K.; Marié, J.-C.; Suh, Y.; Qin, J. *J. Org. Chem.* **2006**, *71*, 7016. (d) Kawasaki, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 16482. (e) Poulsen, T. B.; Alemparte, C.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614. (f) Giampietro, N. C.; Wolfe, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 12907. (g) Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974. (h) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synthesis* **2006**, 137. (i) Chowdari, N. S.; Barbas, C. F. *Org. Lett.* **2005**, *7*, 867. (j) Suri, J. T.; Steiner, D. D.; Barbas, C. F. *Org. Lett.* **2005**, *7*, 3885.

to **8** as a side product of this transformation. Nevertheless, amide **11** could be obtained in five steps from compound **3a**, in 13% overall yield.

Introduction of this piperonyl moiety[14] enables the construction of the polyoxygenated phenanthridone skeleton via an intramolecular Heck cyclization. Compounds **12** and **14** were obtained using cyclization conditions reported by Beller and co-workers, as single diastereomers, without any double bond migration.[15]

In conclusion, we have shown that hydrazines **1**, readily available by an almost quantitative solvent-free ene-reaction from cyclohexadiene, are valuable precursors for desymmetrization reactions. As an example, the use of Sharpless asymmetric dihydroxylation enables a fast and efficient access to several useful chiral building blocks. This approach, based on prochiral dienes bearing a C−N bond, is complementary to the existing desymmetrization strategies unmasking C−Si or C−C stereogenic centers from analogous prochiral precursors. It opens a new route to polyfunctionalized aminocyclohexanes with expanded chemical and stereochemical diversity. Application to the synthesis of more complex alkaloids such as lycoricidine is under investigation and will be reported in due course.

(14) The bromopiperonyl acyl chloride was prepared in four steps from piperonyl alcohol.

(15) For a discussion on bond migration on similar substrates during a Pd-catalyzed cyclisation, see: Von Wangelin, A. J.; Neumann, H.; Gördes, D.; Hübner, S.; Wendler, C.; Klaus, S.; Strübing, D.; Spannenberg, A.; Jiao, H.; El Firdoussi, L.; Thurow, K.; Stoll, N.; Beller, M. *Synthesis* **2005**, 2029.

Acknowledgment. G.E. thanks GlaxoSmithKline and CNRS for a grant.

Note Added after ASAP Publication. This article posted ASAP on May 26, 2009 with errors in the footnotes for Schemes 2 and 5. The final corrected version posted May 29, 2009.

Supporting Information Available: Analytical data for all new compounds and NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900779V