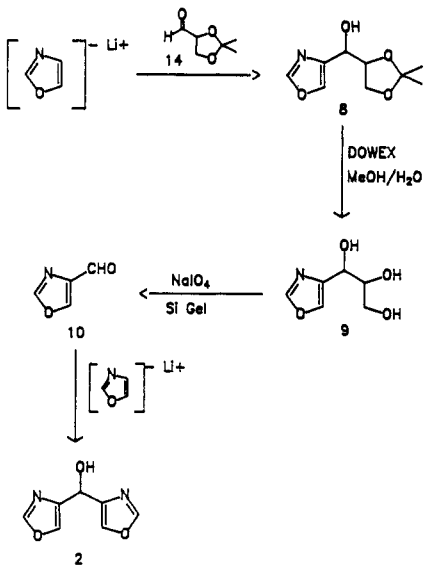

Figure 4. Symmetrical bis(oxazolyl)methanol 2.

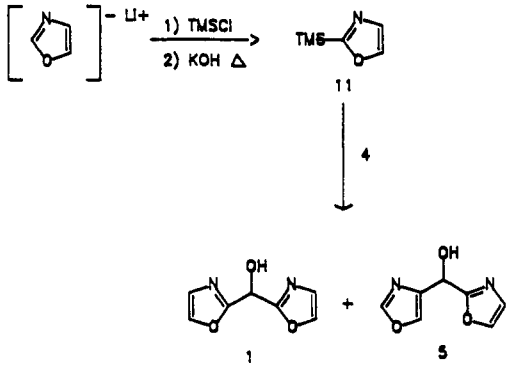

Figure 5. Bis(oxazolyl)methanols 1 and 5.

stereomers. Hydrolysis of the acetonide group is accomplished using Dowex 50 in moist methanol to give a quantitative yield of triol **9**. Oxidative cleavage of **9** using a heterogeneous reagent formed by adsorption of aqueous $NaIO_4$ onto silica gel affords 1,3-oxazole-4-carboxaldehyde (**10**) as a solid in 70% yield after chromatography. Treatment of **10** with 1.3 equiv of lithiooxazole gives **2** in 62% isolated yield.

A low-yielding preparation of **1** is shown in Figure 5. Excess 2-(trimethylsilyl)-1,3-oxazole (**11**) and 1,3-oxazole-2-carboxaldehyde (**4**) are heated neat at 70 °C for 90 min to afford a mixture of **1** and **5** (ca. 1:1, 21% combined yield), which are separable by chromatography. In this sense 2-(trimethylsilyl)-1,3-oxazole behaves as both 2- and 4-lithiooxazole synthons with aldehydes. This is in contrast with literature precedents for thiazole and substituted oxazoles where reaction of 2-TMS derivatives with aldehydes give high-yielding and regiospecific reactions, affording only 2-substituted products.[2,4,6]

In summary, the equilibrium between 2-lithiooxazole and the ring-opened lithium enolate provides the basis for the ambident nucleophilicity observed for "lithiooxazole". Highly reactive, oxophilic electrophiles such as TMS-Cl and D_2O react at oxygen, aldehydes react at the 4-position, and most other weaker electrophiles either react at the 2-position or do not react. In all instances high regioselectivity is observed, i.e. mixtures of 0-, 2- and 4-substituted products are typically not found. The unusual preference for 4-substitution seen with aldehydes appears to be related to their low oxophilicity and their ability to react at lower temperatures. The fact that traces of the 2-substituted product, **13b**, are seen when benzaldehyde is allowed to react with lithiooxazole at room temperature is supportive of this regioselectivity hypothesis. By reacting 2-(trimethylsilyl)-1,3-oxazole with aldehydes it is possible to alter the regioselectivity of addition, affording low yields of both 4- and 2-substituted products. The isomeric bis(oxazolyl)methanols, **1**, **2** and **5**, may be prepared from "lithiooxazole" by three different strategies.

Registry No. **1**, 130551-89-2; **2**, 130551-90-5; **4**, 65373-52-6; **5**, 130551-91-6; **6**, 130551-92-7; **7a**, 130551-93-8; **8** (isomer 1), 130551-94-9; **8** (isomer 2), 130551-95-0; **9**, 130551-96-1; **10**, 118994-84-6; **11**, 120629-79-0; **12**, 130551-97-2; **13a**, 130551-98-3; **13b**, 130552-00-0; **14**, 5736-03-8; **15**, 67245-00-5; **16**, 130551-99-4; BuCHO, 110-62-3; PhCHO, 100-52-7; PhCOPh, 119-61-9; HCO_2Et, 109-94-4; TMSCl, 75-77-4; BuI, 542-69-8; $PhCH_2Br$, 100-39-0; $(EtO)_2CO$, 105-58-8; $HCONMe_2$, 68-12-2; oxazole, 288-42-6.

Supplementary Material Available: Experimental details for representative reactions, spectral data, analytical data, and ^1H NMR spectra of new compounds (25 pages). Ordering information is given on any current masthead page.

Synthesis of Secondary Amines by Rhodium Catalyzed Hydrogenation of Nitriles

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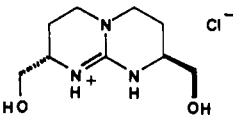
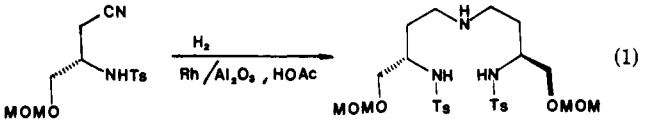
Received May 1, 1990

We recently reported the preparation of the first example of a C_2 symmetric, chiral guanidine **1** and its enantiomer starting from L- or D-asparagine, respectively.[1] These chiral guanidines complex aromatic carboxylate anions[2] and phosphate containing guests.[3,4] The high



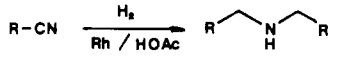
1

efficiency of the reported syntheses relied on the one-step assemblage of a protected triamine dimer by a rhodium-catalyzed hydrogenation of nitrile **2** (eq 1).



(1)

As part of a broader program aimed at developing chiral anion receptors based on guanidine subunits, we examined the generality of this secondary amine synthesis for the preparation of the key synthetic intermediates (eq 2).



(2)

The catalytic hydrogenation of nitriles is usually complicated by the formation of mixtures of primary, secondary, and tertiary amines.[5] The composition of the reduction products depends markedly on the nature of the

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‡ Instituto de Química Orgánica, CSIC.

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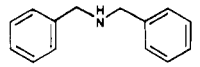
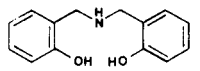
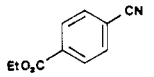
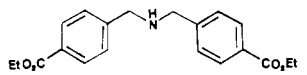
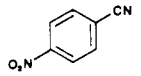
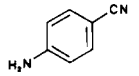
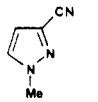
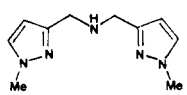
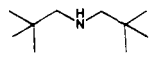
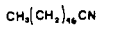
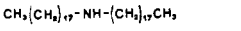
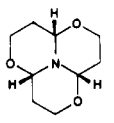
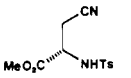
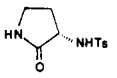
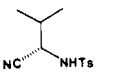
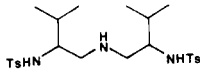
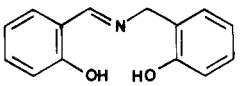
Table I[a]

entry	nitrile	amine	yield, %
1			85
2			83
3			72
4			95
5			79[b]
6			80[c]
7			78[c]
8			70
9			76
10[d]			70

[a] Unless otherwise stated, 5% Rh on alumina was used in the reduction. [b] Characterized as the *N*-acetyl derivative. [c] Isolated as the hydrochloride. [d] The hydrogenation was performed over 5% Rh on carbon catalyst.

metal catalysts, on the reaction temperature and hydrogen pressure, and on the nitrile structure.[5] For the conversion of nitriles into primary amines under mild conditions (room temperature, 2–3 atm of hydrogen), the use of rhodium catalysts in the presence of ammonia in alcoholic solvents has been recommended.[6,7] In the absence of ammonia, the catalytic hydrogenation has been reported to lead instead to mixtures, with secondary amines as the major products.[5-7] In our hands such a procedure proved to be unreliable, and complex mixtures of amines were obtained when methanol or ethanol was used as solvent. In this paper we report that the preparation of secondary amines from nitriles can be carried out with rhodium catalysts in acetic acid under ambient conditions in good yields.

The results of the catalytic hydrogenation of nitriles with rhodium on alumina or carbon are summarized in Table I. The reaction appears to be general. Aromatic (entries 1–3), heteroaromatic (entry 5), and aliphatic nitriles (entries 6, 7, and 10) are readily hydrogenated to secondary amines under 1 atm of hydrogen at room temperature in glacial acetic acid for 20–30 h. Presumably the acidic solvent promotes the condensation of the primary amines with the aldimines leading to the desired secondary amines. In one instance (entry 2) the intermediate imine **3** could be isolated as a byproduct. None of the tertiary amines were detected (however, see below), although small amounts of primary amines were observed in some instances in the crude reaction mixtures. These byproducts were minimized by increasing the nitrile concentration.[5b]

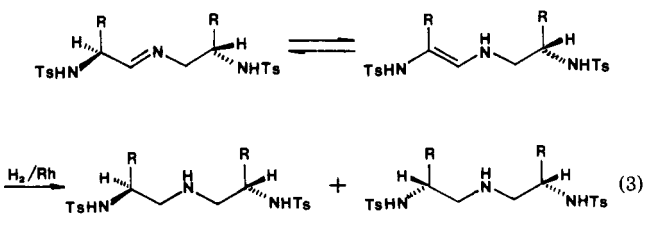


3

The hydrogenation tolerates OH, CO_2Et, and NHTs functional groups (entries 2, 3, and 10) and does not seem to be sensitive to steric hindrance in the α-position of the nitrile (entries 6 and 10). However, not unexpectedly, an aromatic nitro group is reduced in high yield under the reaction conditions (entry 4).

Surprisingly, while the reduction of 2-hydroxybenzonitrile proceeded uneventfully (entry 2), the aliphatic analogue, 3-hydroxypropanonitrile, affords the interesting tertiary amine **4** as a single isomer (entry 8), as a result of the trimerization of the intermediate primary imine. The structure was assigned on the basis of its 300-MHz ^1H NMR spectrum, which showed coupling contants between the C-2, C-3, and C-4 protons as expected for a tetrahydro[1,3]oxazine ring in the chair conformation.[8] Furthermore, the ^{13}C NMR spectrum showed only three carbon resonances of the C_3 symmetric amine. Consistently with the assigned trans-fused structure, with a syn arrangement of the three oxygens and the nitrogen lone electron pair, protonation with trifluoroacetic acid yields a stable ammonium salt. To the best of our knowledge, **4** constitutes the first member of this heterocyclic ring system. The formation of a secondary amine was also prevented by formation of a lactam in the reduction of the β-cyanoalanine derivative **5** (entry 9).

The catalytic hydrogenation of optically pure nitrile **6**, obtained in four steps from L-valine, was also examined. In this case, the intermediate imine **7**, formed in the hydrogenation of **6**, could exist in equilibrium with the enamine **8**, yielding, after hydrogenation, a mixture of (*R,S*)-**9** and its *meso* isomer **10** (eq 3). Alternatively, complete



(3)

racemization could take place at the primary imine stage

(1) Echavarren, A.; Galán, A.; de Mendoza, J.; Salmerón, A.; Lehn, J.-M. *Helv. Chim. Acta* **1988**, *71*, 685.
(2) Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994.
(3) Deslongchamps, G.; Galán, A.; de Mendoza, J.; Rebek, J., Jr., manuscript in preparation.
(4) Schmidtchen, F. P. *Tetrahedron Lett.* **1989**, *30*, 4493.
(5) For reviews on the catalytic hydrogenation of nitriles, see: (a) Cerveny, L., Ed. Catalytic Hydrogenation. In *Studies in Surface Science and Catalysis*; Elsevier: Amsterdam, 1986; Vol. 27, Chapter 4. (b) Rylander, P. *Catalytic Hydrogenation in Organic Syntheses*; Academic: New York, 1979; Chapter 8. (c) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*; Wiley-Interscience: New York, 1978; Chapter 6.
(6) Freifelder, M. *J. Am. Chem. Soc.* **1960**, *82*, 2386.
(7) Reduction of 3-indoleacetonitrile in the absence of ammonia was reported to yield predominantly the secondary amine, contaminated with some tryptamine (yield not stated). In other examples the yield of secondary amine ranged from 10 to 20%, in reactions run in the presence of ammonia.[6]
(8) Crabb, T. A.; Hall, M. J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1379.

leading to racemic **9** and *meso*-**10** by an analogous process. In the event, the catalytic hydrogenation of **6** proceeded smoothly over Rh on carbon, which gave more reproducible results, furnishing an inseparable mixture of **9** and **10** (entry 10). Although variable optical rotations were obtained, analysis of the ^{1}H NMR spectrum after the addition of the chiral shift reagent (+)-Eu(tfc)$_3$[9] gave rise to a similar splitting of the *N*-tosyl methyl resonances to that shown with the secondary amines derived from racemic nitrile (*rac*-**6**), prepared from *rac*-valine. The ratio between the *d*, *l* and *meso* secondary amines was estimated to be approximately 1:1 by integration of the NH protons of the corresponding *N*-acetyl derivatives in a ^{1}H NMR spectrum measured at 50 °C in $(CD_3)_2SO$. At lower temperatures or in deuteriochloroform solutions the spectra were complicated by the presence of several rotamers. Similarly, the presence of amide rotamers precluded any accurate determination of the diastereoisomeric excess based on the analysis of the ^{1}H or ^{19}F NMR spectra of the derived Mosher amides.[10]

In summary, the catalytic hydrogenation of nitriles to secondary amines under ambient conditions has been described. This synthetic method could be particularly useful for the rapid assemblage of functionalized subunits in the preparation of macrocyclic structures.

Experimental Section

General Procedure for the Catalytic Hydrogenation of Nitriles. A mixture of nitrile (0.35 mmol) in glacial acetic acid (3 mL) and 5% rhodium on alumina (400 mg) was stirred at 23 °C under 1 atm of H_2 for 24–30 h. The progress of the reaction was monitored by TLC. The resulting suspension was filtered through Celite, and the filtrate was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. In entries 6 and 7 the crude secondary amine was treated with 1 M HCl in methanol at 23 °C for 1 h, followed by evaporation of the solvent to give the amine hydrochloride. Isolated yields of pure amines are shown in Table I.

Acknowledgment. This work was supported by the "Comisión Asesora de Investigación Científica y Técnica" (CAICYT, Grant 84-0410). We gratefully acknowledge Prof. J. Elguero for a gift of 3-cyano-1-methylpyrazole and A. Salmerón for some hydrogenation experiments.

Supplementary Material Available: Experimental details and spectroscopic data for (*S*)- and (*R*,*S*)-*N*-tosylvaline, *N*-tosylvalinamide, and the compounds in Table I and ^{1}H NMR and COSY spectra for amine 4 (9 pages). Ordering information is given on any current masthead page.

(9) (+)-Eu(tfc)$_3$ = europium(III) tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato].

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Synthesis of Castasterone and Formal Synthesis of Brassinolide from Stigmasterol via a Selenosulfonation Approach

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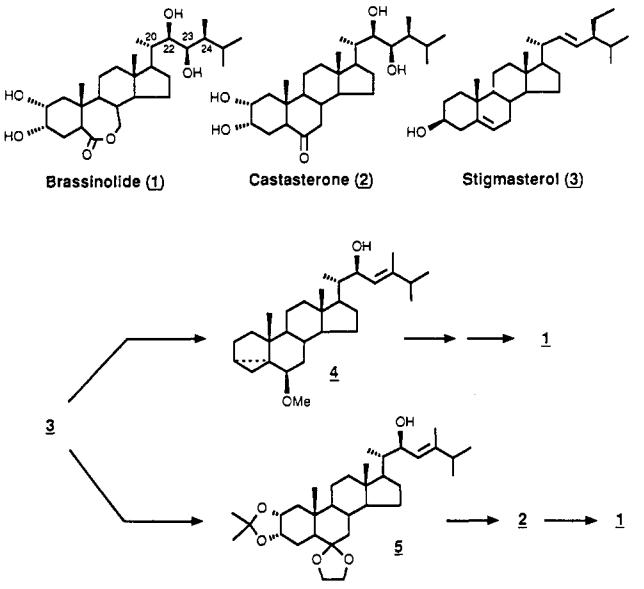
Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

Received May 14, 1990

Brassinolide (**1**) is a steroidal plant growth-promoter that was first isolated by Grove and co-workers[1] from *Brassica napus* L. pollen in 1979. Its low abundance in natural sources and intriguing structure have made it the target of several syntheses.[2,3] The unusual B-ring lactone and the four contiguous chiral centers at C-20, C-22, C-23, and C-24, including the vicinal diol at C-22 and C-23, are structural features that require special attention. Certain related sterols such as castasterone (**2**) exhibit similar activity,[4] and their syntheses are also of interest.[3c,f,k]

Scheme I



We recently reported the preparation of the allylic alcohol **4** from stigmasterol (**3**)[5] using selenosulfonation methodology.[6] Alcohol **4** has also been prepared by other methods[3a,n] and is a useful intermediate for the elaboration of brassinosterol side chains. We now report the selenosulfonation-based preparation of the more highly elaborated intermediate **5**, which provides more direct access

(1) Grove, M. D.; Spencer, G. F.; Rohwedder, W. K.; Mandava, N.; Worley, J. F.; Warthen, J. D., Jr.; Steffens, G. L.; Flippen-Anderson, J. L.; Cook, J. C., Jr. *Nature (London)* **1979**, *281*, 216.

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