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Partial Reduction of Annulated Heterocycles as a General Route to Medium Rings Containing Oxygen and Nitrogen

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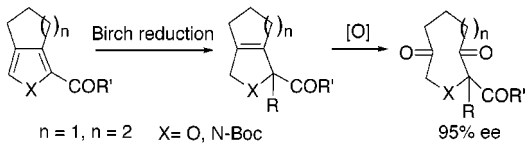
ABSTRACT



The preparation of annulated furans and pyrroles is described as part of a general strategy for the synthesis of medium ring heterocycles. After Birch reduction, the corresponding dihydro compounds were oxidatively cleaved to produce medium ring ethers and amines in an efficient manner. This methodology was successfully applied to the formation of eight- and nine-membered cyclic ethers and nine-membered cyclic amines. Attaching a chiral auxiliary (bismethoxymethylpyrrolidine) to the furan allowed the formation of nine-membered ethers in 95% ee.

The abundance of medium ring heterocycles, containing oxygen and nitrogen, in natural products continues to ensure that they are popular targets for synthetic chemists.[1] Indeed, some of these compounds, such as the eleutherobins and the sarcodictyins,[2] have impressive and potentially useful biological activity.

Synthetic routes to medium ring heterocycles which involve direct ring closure are often slow and are hampered by unfavorable entropies and enthalpies of reaction.[3] One only needs to look at the synthesis of brevetoxin B by Nicolaou[4] to appreciate both the challenges associated with the synthesis of medium ring ethers and the elegant solutions that have been developed in response.

Ring enlargement protocols are also popular routes to medium rings, and one potentially useful variant does not involve a ring closure reaction but, instead, relies on the synthesis of a fused ring system which has the potential to become a medium ring after oxidative cleavage of an internal alkene, see **2** (Figure 1).[5] Of course, access to the medium ring precursor **2** is relatively easy to accomplish providing

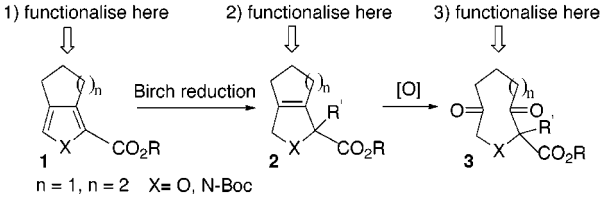


Figure 1.

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(1) For recent work in this area, see: Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc*. **1999**, *121*, 5653, and references therein.

(2) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc*. **1997**, *119*, 8744.

(3) For a pertinent discussion of the issues surrounding medium ring synthesis, see: Eliel, E. L. *Stereochemistry of Organic Compounds*; John Wiley: New York, 1994.

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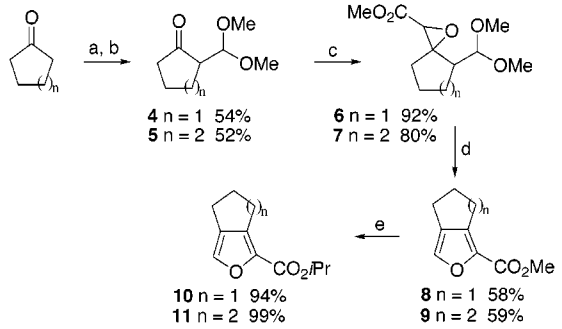
one can achieve a Birch reduction of the appropriate annulated furans and pyrroles (i.e. **1**, X = O, NBoc). In this case, the successful implementation of this strategy reveals three distinct tactics for further functionalization of the medium rings: (1) we can prepare heterocycles with more elaborate annulated rings; (2) we can functionalize the heterocycle during or immediately after the Birch reduction; (3) we should be able to derivatize the cyclic diketone products after oxidative cleavage of the alkene unit. Of course, it is the combination of all or some of these opportunities that will give rise to a powerful and versatile method for medium ring synthesis. In this paper we wish to communicate the results of our initial studies confirming the viability of this approach.

Our studies began with the synthesis of cyclic ethers. Their furan progenitors were prepared from cyclopentanone and cyclohexanone, respectively, using a modification of an established method, Scheme 1.[6] Initial Claisen condensation

Scheme 1[a]

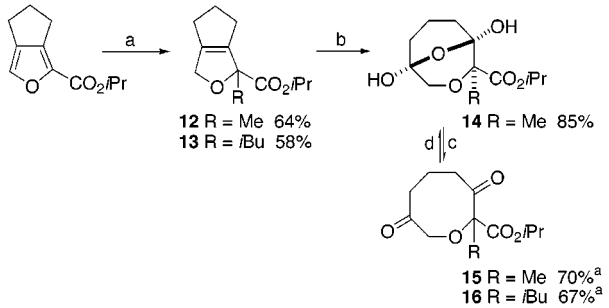


[a] Reagents and conditions: (a) NaH (1.0 equiv), HCO_2Et (2.0 equiv), Et_2O, 0 °C to reflux, 2 h; (b) EtOH, CH_3COCl (2 equiv), MeOH (excess), 0 °C to rt, 16 h; (c) $ClCH_2CO_2Me$ (1.6 equiv), NaOMe (1.5 equiv), Et_2O, −10 °C to rt, 20 h; (d) CSA (1.0 equiv), toluene, reflux, 6-8 h; (e) $Ti(OEt)_4$ (1 equiv), i-PrOH (excess), reflux, 7 h.

was followed by formation of two dimethylacetals, **4** and **5**; subsequent Darzen's condensation gave the two epoxides **6** and **7** as a mixture of diastereoisomers. These epoxides are at the correct oxidation level for furan formation, and this was accomplished by heating in toluene with CSA. Finally, the methyl esters **8** and **9** were transformed into isopropyl analogues **10** and **11** in excellent yield (this was necessary because hindered esters are less prone to nucleophilic attack in the Birch reduction, vide infra).

With multigram quantities of the two annulated furans **10** and **11** at our disposal, we attempted Birch reductive alkylation reactions on the $n = 1$ series, quenching with two different electrophiles, Scheme 2.[7] Both reactions worked

Scheme 2[a]



[a] Reagents and conditions: (a) Li (4.0 equiv), NH_3 (l), THF, −78 °C, bis(2-methoxyethyl)amine (20 equiv), then isoprene, then RI (10 equiv); (b) O_2/O_3, CH_2Cl_2, −78 °C, 2 h, then DMS; (c) toluene, 4Å molecular sieves, Dean−Stark reflux, 36 h; (d) column chromatography using silica. [a]Yields based on Birch reduced starting materials **12** and **13**; compound **15** could not be completely purified.

well (even with isobutyl iodide, a relatively unreactive electrophile) and show the potential that this method holds for the introduction of a variety of different groups at the C-2 position. It was found that reduction of the trisubstituted furans required relatively long reaction times and that using the additive bis(2-methoxyethyl)amine reduced nucleophilic attack of amide anion at the ester group.[8] The dihydrofurans **12** and **13** were then cleaved with ozone (using DMS workup) to give eight-membered ring ethers. We found that the diketones **15** and **16** were each in equilibrium with a corresponding bicyclic hemiacetal; this equilibrium could be shifted to either side by chromatography on silica (to hydrate the ketone) or azeotroping in toluene (to dehydrate the system). The structure of hydrate **14** was secured by X-ray crystallography, Figure 2.[9]

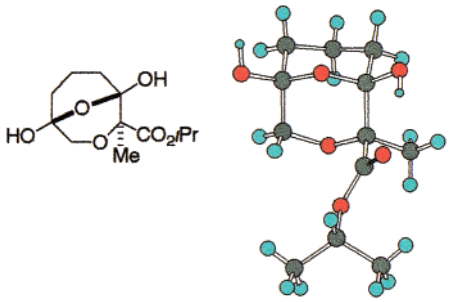


Figure 2.

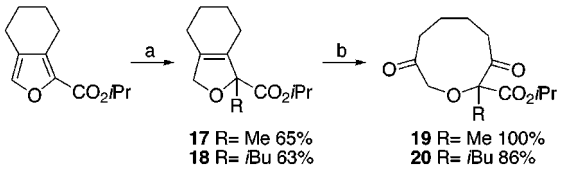
In a similar manner, Birch reduction/alkylation of **11** gave the two 6,5-fused dihydrofurans **17** and **18**, Scheme 3.[10] Subsequent reaction with ozone and DMS,[11] as before,

(4) (a) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. (b) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173.

(5) For related approaches, see: (a) Elliot, M. C.; Moody, C. J.; Mowlem, T. J. *Synlett* **1993**, 909. (b) Oishi, T.; Shoji, M.; Maeda, K.; Kumahara, N.; Hirama, M. *Synlett* **1996**, 1165. (c) Oishi, T.; Maruyama, M.; Shoji, M.; Maeda, K.; Kumahara, N.; Tanaka, S.-I.; Hirama, M. *Tetrahedron* **1999**, *55*, 7471.

(6) (a) Burness, D. M. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p, 649. (b) Pye, P. J. Ph.D. Thesis, University of Texas at Austin, 1995. (c) Datta, A.; Pooranchand, D.; Ila, H.; Junjappa, H. *Tetrahedron* **1989**, *45*, 7631.

Scheme 3[a]

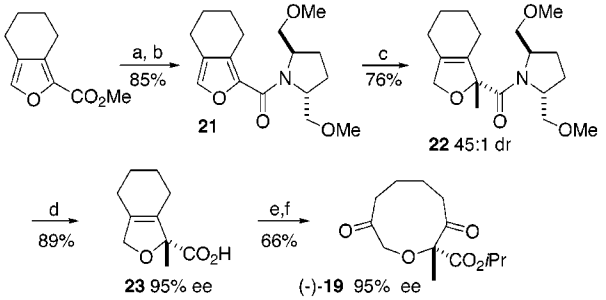


[a] Reagents and conditions: (a) Li (4.0 equiv), NH_3(l), THF, −78 °C, bis(2-methoxyethyl)amine (33 equiv), then isoprene, then RI (20 equiv); (b) O_2/O_3, CH_2Cl_2, −78 °C, 1.5 h, then DMS, rt, 16 h.

generated two nine-membered cyclic ethers in excellent yield, without any observable formation of hydrates.[12]

The methodology described herein is also amenable to the production of enantiopure compounds if an auxiliary (*R,R*-bismethoxymethylpyrrolidine) is attached to the C-2 acyl group of the furan prior to reduction, compound **21**, Scheme 4. Our earlier work was concerned with the partial reduction

Scheme 4[a]



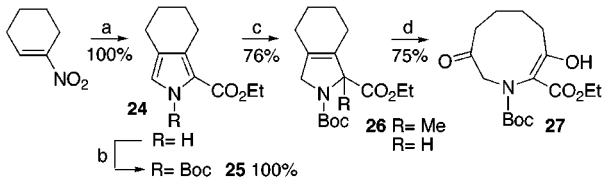
[a] Reagents and conditions: (a) MeOH:H_2O (9:1), KOH, Δ, 3 h; (b) (*R,R*)-(+)-2,5-bismethoxymethylpyrrolidine (1 equiv), Et_3N (2 equiv), CH_2Cl_2, BOP-Cl; (c) Li (4 equiv), NH_3(l), THF, −78 °C, bis(2-methoxyethyl)amine (20 equiv), then isoprene, then MeI (10 equiv); (d) 2 M HCl (aq.), Δ, 2.5 h; (e) EDCl (1 equiv), DMAP (cat.), iPrOH, CH_2Cl_2, rt; (f) O_2/O_3, CH_2Cl_2, −78 °C, then DMS.

of 2-furoic acids and, using bismethoxymethylpyrrolidine as an auxiliary, had shown that an *ortho* methyl substituent was essential for high levels of stereoselectivity as it sets the geometry of the enolate formed during the Birch reduction.[13] Fortunately, in this case, the annulated ring is sufficiently bulky to allow formation of a single enolate isomer (we presume it is *trans*) and we observed high diastereoselectivity upon reductive alkylation of **21**, Scheme 4. In fact, GC analysis of the crude reaction mixture from which compound **22** was isolated showed that it was formed as a 45:1 mixture of diastereoisomers. After cleavage of the auxiliary, we re-analyzed the acid **23** and showed it to be of 95% ee (again using GC and in comparison with a racemic standard). To complete the sequence, we reattached the isopropyl ester to allow comparison with the sample shown in Scheme 3. After ozonolysis, the ester (−)-**19** was isolated in good yield; although we were unable to measure directly the enantiomeric excess of this material, it seems reasonable to assume that it is identical with the acid **23** from which it originated (i.e. 95% ee).

The relative stereochemistry of **22** (and therefore the absolute stereochemistry of **23**) was determined by X-ray crystallographic analysis of a crystalline derivative of **23**. The sense of stereoselectivity thus displayed during the Birch reductive alkylation of **21** is in accord with the model that we have previously presented for related systems.[12]

Finally, we applied our methodology to the partial reduction of annulated pyrrole **25** (easily prepared in two quantitative yielding steps, Scheme 5[14]). Birch reductive alkylation

Scheme 5[a]



[a] Reagents and conditions: (a) EtO_2CCHNC, DBU; (b) $(Boc)_2O$, NaH; (c) Li (4 equiv), NH_3(l), THF, −78 °C, bis(2-methoxyethyl)amine (10 equiv), then isoprene, then (aq.) NH_4Cl; (d) O_2/O_3, CH_2Cl_2, −78 °C, then DMS.

of **25**, quenching with methyl iodide, proceeded well to give **26** (R = Me, 83%).[15] However, we found that the alkene group within this pyrroline was resistant to ozonolysis at low temperature and gave multicomponent mixtures at higher

(7) (a) Coggiola, I. M. *Nature* **1963**, *200*, 954. Kinoshita, T.; Miwa, T. *J. Chem. Soc., Chem. Commun.* **1974**, 181. (b) Masamune, T.; Ono, M.; Matsue, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 491. (c) Birch, A. J.; Slobbe, J. *Tetrahedron Lett.* **1975**, 627. (d) Birch, A. J.; Slobbe, J. *Tetrahedron Lett.* **1976**, 2079. (e) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505. (f) Ohta, Y.; Tamura, M.; Tanaka, R.; Moriomoto, Y.; Yoshihara, K.; Kinoshita, T. *J. Heterocycl. Chem.* **1998**, *35*, 461. See also ref 9.

(8) Donohoe, T. J.; Guyo, P. M.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **1998**, *39*, 3075.

(9) CCDC deposition number for **14** is 156092.

(10) **Representative experimental procedure:** Lithium (27 mg, 3.8 mmol) was added to freshly distilled ammonia (50 mL) and allowed to stir at −78 °C under an atmosphere of nitrogen for 2 h before the addition of bis-(2-methoxyethyl)amine (5 mL, 30 mmol). Compound **11** (200 mg, 0.96 mmol) was dissolved in THF (25 mL) and added to the reaction mixture after 5 min. The resultant solution was allowed to stir at −78 °C for 2.5 h before the addition of isoprene (50 μL), immediately followed by methyl iodide (2 mL, 32 mmol). After an additional 1 h, the resultant bright yellow solution was treated with a saturated ammonium chloride solution (5 mL) before being allowed to warm to room temperature over 16 h. The reaction mixture was extracted into diethyl ether (3 × 50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford a yellow oil. Purification by chromatography (silica, petroleum ether−diethyl ether, 9:1 v/v) afforded compound **17** (140 mg, 65%) as a colorless oil.

(11) Compound **17** (50 mg, 0.22 mmol) was dissolved in dichloromethane (15 mL) and cooled to −78 °C under an atmosphere of O_2. Ozone was generated and bubbled through the reaction mixture for 1.5 h. The resultant blue solution was saturated with O_2 for 10 min before the addition of dimethyl sulfide (0.16 mL, 2.2 mmol). The reaction mixture was allowed to warm to room temperature over 16 h. The resultant solution was washed with brine (2 × 5 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford compound **19** (59 mg, 100%) as a pale yellow oil which did not require further purification.

(12) Care must be taken with these compounds as an intramolecular aldol reaction takes place on exposure to silica.

temperatures. Other methods of bond cleavage (e.g., Lemieux oxidation) were not successful in producing a nine-membered ring. A solution to this problem was found via formation of **26** (R = H) by protonation of the Birch reduction (76%). The alkene could then be cleaved in a standard manner to furnish the corresponding diketone, which existed entirely as the enol tautomer, **27**.

To conclude, this methodology provides a convenient route to substituted medium ring ethers and amines which have ample potential for further functionalization. Moreover, employing a chiral auxiliary laiden aromatic heterocycle leads to the formation of cyclic ethers with a very high enantiomeric excess. Future work will concentrate on derivatization reactions of these medium ring compounds and application of our methodology to the synthesis of biologically important targets.

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Supporting Information Available: Detailed spectroscopic data for new compounds and representative experimental procedures, plus X-ray data for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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