ORGANIC LETTERS

2002
Vol. 4, No. 18
3059−3062

Synthesis of Enantiopure Dihydropyranones: Aldol-Based Ring Expansion of Dihydrofurans

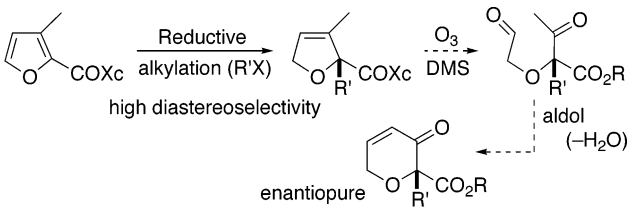
Timothy J. Donohoe,*,† Ali Raoof,‡ Graeme C. Freestone,† Ian D. Linney,§ Andrew Cowley,†,|| and Madeleine Helliwell‡,||

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, U.K., Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, U.K., and The James Black Foundation, 68 Half Moon Lane, Dulwich, London SE24 9JE, U.K.

timothy.donohoe@chem.ox.ac.uk

Received June 13, 2002

ABSTRACT



The stereoselective Birch reduction of 3-methyl-2-furoic acids using a readily available chiral auxilairy is described; by coupling this process to an oxidative cleavage/aldol ring closure sequence we were able to produce highly functionalized and enantiopure dihydropyranones in high yield. This sequence has ample flexibility built into it, either by the use of different electrophiles during reductive alkylation or by subsequent derivatization of the dihydropyranone after ring expansion.

Recently, we have published the results of our studies into the partial reduction of aromatic heterocycles.[1] While most attention has been paid to controlling the stereo- and chemoselectivity of such a process, we have become interested in further transformations of the dihydro-compounds produced by such methodology. This facet of our research is best illustrated by our conversion of annulated dihydrofurans into eight- and nine-membered rings by an oxidative cleavage strategy, Figure 1.[2]

One of the continuing problems that we encountered during preparation of nine-membered rings (containing both oxygen and nitrogen) was intramolecular aldol condensation of the diketones formed after cleavage by ozonolysis, Scheme 1. In fact, 1,5-dicarbonyl compounds such as **2** were even sensitive to the silica gel used for chromatography and had to be handled with care if the integrity of the nine-membered ring was to be maintained. The regiochemistry of the aldol product **3** was assigned by X-ray crystal structure of an aldol adduct **5** that did not readily dehydrate and form an enone.

However, we quickly realized that this process could be harnessed by reductively alkylating 3-methyl-2-furoic acids, followed by oxidative cleavage[3] and then (dehydrating) aldol

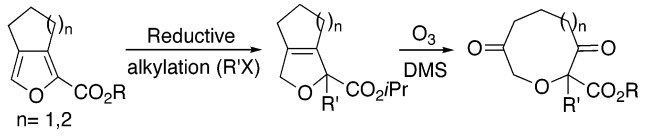


Figure 1.

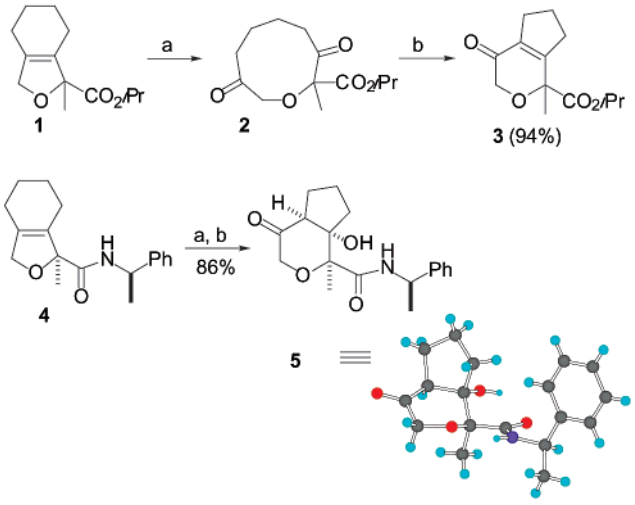
† University of Oxford.
‡ University of Manchester.
§ James Black Foundation.
|| To whom correspondence regarding the crystal structures should be addressed.

(1) (a) Donohoe, T. J.; Guyo, P. M. *J. Org. Chem.* **1996**, *61*, 7664. (b) Donohoe, T. J.; Guyo, P. M.; Beddoes R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 667. (c) Donohoe, T. J.; McRiner A. J.; Sheldrake, P. *Org. Lett.* **2000**, *2*, 3861. (d) Donohoe, T. J.; McRiner, A. J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1435.

(2) Donohoe, T. J.; Raoof, A.; Linney, I. D.; Helliwell, M. *Org. Lett.* **2001**, *3*, 861.

10.1021/ol0263595 CCC: $22.00
Published on Web 08/02/2002

Scheme 1[a]



[a] Reagents and conditions: (a) O_2/O_3, CH_2Cl_2, −78 °C, then DMS; (b) SiO_2.

ring closure to give enantiopure dihydropyranones, Figure 2.[4] In this scenario, there is only one likely regiochemical outcome from the aldol reaction of postulated keto-aldol **6**.

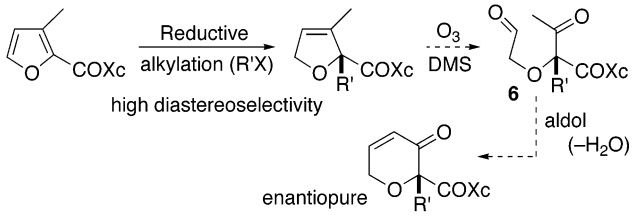
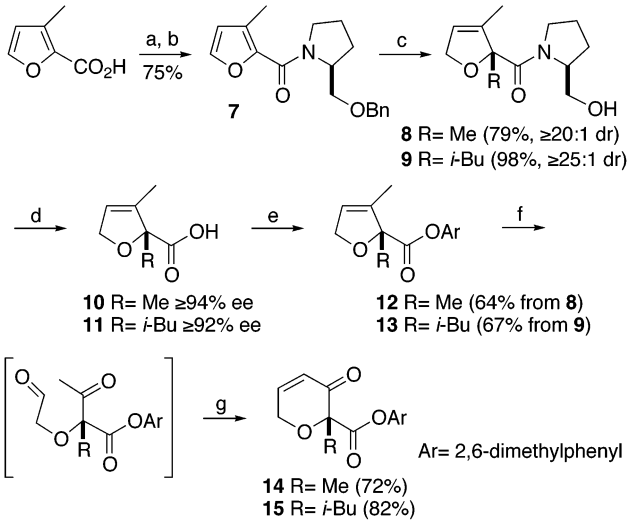


Figure 2.

Another big advantage of this protocol is that 3-substituted furans are excellent substrates for the stereoselective Birch reduction using two different auxiliaries (Xc);[5] this, of course, should enable us to prepare the corresponding dihydropyranones in enantiomerically pure form after ring expansion. We investigated stereoselective reduction and ring cleavage using *O*-benzylprolinol as an auxiliary[5] because it is significantly easier to obtain than the bis-methoxymethylpyrrolidine alternative.[6]

Therefore, we took commercially available 3-methyl-2-furoic acid, coupled it to (+)-*S*-prolinol, and then benzylated the hydroxyl group to give **7** in excellent overall yield, Scheme 2. Reductive alkylation of **7** in liquid ammonia proceeded well and we chose two electrophiles to illustrate that both reactive (MeI) and relatively unreactive (^{i}BuI) alkylating agents work in this reaction. In both cases, the diastereoselectivity was very high (measured by ^{1}H NMR spectroscopy on the crude reaction mixtures and compared against a 1:1 mixture of diastereoisomers).[7] Moreover, the acid **10**, released from **8**, was shown to have ≥94% ee by chiral shift NMR experiments in the presence of α-methylbenzylamine (measured against a racemic standard). Given that the dr of **9** is secure, the enatiomeric excess of **11** can be assumed to be 92% by analogy. The absolute stereochemistry of both **10** and **11** was proven by correlation of their sign of optical rotation to known compounds.[5]

Scheme 2[a]



[a] Reagents and conditions: (a) $SOCl_2$ then (*S*)-prolinol, CH_2Cl_2, NaOH; (b) NaH, BnBr, TBAI, THF; (c) Li (4 equiv), NH_3 (l), THF, −78 °C, then isoprene, then MeI or *i*-BuI (10 equiv); (d) 2 M HCl (aq), Δ, 2.5 h; (e) 2,6-dimethylphenol, EDCl (2 equiv), DMAP (cat.), CH_2Cl_2, rt; (f) O_2/O_3, CH_2Cl_2, −78 °C, then DMS; (g) CSA, toluene or xylene, Δ.

Despite several attempts, we had no success in cleaving the alkene with an auxiliary still attached to the molecule (**9**) and multicomponent mixtures were obtained in each case. Therefore, the prolinol moiety was cleaved under mild acidic conditions and coupled to 2,6-dimethylphenol to provide an inert but easily removable group on the C-2 carbonyl (Scheme 2). Oxidative cleavage of **12** and **13** with ozone gave the keto-aldehydes after DMS workup. Although these aldehydes were not isolated, they could be observed by ^{1}H NMR spectroscopy and were treated directly with CSA, which promoted a (dehydrating) aldol reaction to form the six-membered ring system directly and in one pot.[8] Basic

(3) See Landais, Y.; Zekri, E. *Tetrahedron Lett.* **2001**, *42*, 6547.
(4) See: (a) Danishefsky, S.; Cavanaugh, R. *J. Am. Chem. Soc.* **1968**, *90*, 520. (b) Danishefsky, S.; Cain P.; Nagel, A. *J. Am. Chem. Soc.* **1975**, *97*, 380. (c) Danishefsky, S.; Cain, P. *J. Org. Chem.* **1975**, *40*, 3606. (d) Kutney, J. P.; Grice, P.; Piotrowska, K.; Rettig, S. J.; Szykula, J.; Trotter, J.; Chu, L. V. *Helv. Chim. Acta* **1983**, *66*, 1820.
(5) Donohoe,T. J.; Calabrese, A. A.; Stevenson, C. A.; Ladduwahetty, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3724.
(6) (a) Donohoe, T. J.; Helliwell, M.; Stevenson C. A.; Ladduwahetty, T. *Tetrahedron Lett.* **1998**, *39*, 3071. (b) Donohoe, T. J.; Calabrese, A. A.; Guillermin, J.-B.; Walter, D. S. *Tetrahedron Lett.* **2001**, *42*, 5841.
(7) More accurate measurements on the crude mixture means that we have revised the diastereoselectivity of the reaction **7** → **8** upwards from 13:1 to 20:1; see ref 5.

aldol conditions (Et_3N, Δ) were also capable of producing **15**, although the overall yield was lower. Given their origin, it is reasonable to assume that the enantiomeric excesses of the six-membered ring compounds **14** and **15** are as equally high as **10** and **11**, the five-membered progenitors.

The sense of stereoselectivity displayed during the reductive alkylation step is noteworthy and consistent with the formation of an *E*-enolate **A** (after addition of two electrons and a proton to **7**, Figure 3).

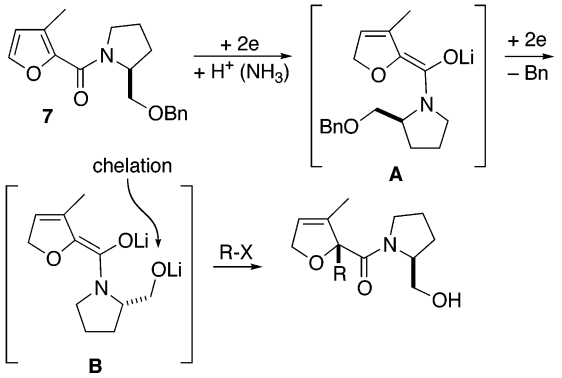
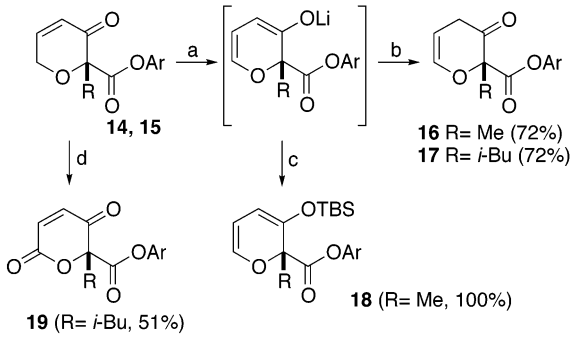


Figure 3.

To achieve high stereoselectivity, chelation control is necessary, and the (sacrificial) benzyl group is a source of such a chelating oxygen, generated in situ, **B**.[5,9] We presume that coordination of the two O−Li species is instrumental in preventing rotation about the C−N bond and so providing a basis for discrimination between the two enolate faces.[10] Under the low-temperature regimen, the lithium alkoxide that remains is unreactive toward the alkylating agent and is simply protonated upon workup.

Next, we investigated some of the reactivity of the dihydropyranones produced via this sequence. For example, formation of an extended enolate with LDA, followed by kinetic protonation at C-4[11] gave the enol ethers **16** and **17**, Scheme 3. Our ability to migrate the alkene in this manner

Scheme 3[a]

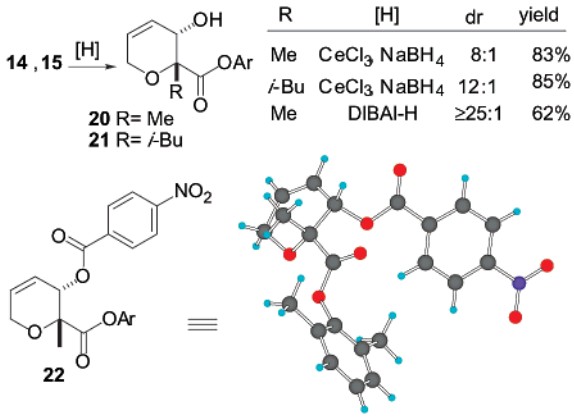


[a] Reagents and conditions: (a) LDA, THF, −78 °C; (b) NH_4Cl (aq); (c) TBSOTf; (d) PCC, *t*-BuOOH.

has clear ramifications for further functionalization at C-6. In fact, the extended enolate could be trapped with a silylating agent to provide diene **18** in good yield. Moreover, the enone could also be oxidized to the corresponding lactone **19** with PDC/*t*-BuOOH,[12] again increasing the flexibility of the sequence to encompass sugar substitution patterns.

Finally, we also investigated reduction of the C-3 keto group and found that excellent levels of diastereoselectivity could be achieved for 1,2-reduction of both **14** and **15**, especially when using a bulky hydride source and low temperatures, Scheme 4. The lower yield recorded with

Scheme 4



DIBAl-H as a nucleophile reflects competing attack at the ester carbonyl in the presence of excess reagent. The sense of diastereoselectivity was confirmed by X-ray crystallography on a *p*-nitrobenzoate derivative **22** and is consistent with axial attack of hydride on a conformation of the ketone that places the bulky alkyl groups equatorial and the ester group axial.

(8) **Representative Experimental Procedure.** Dihydrofuran **12** (3.31 g, 13.5 mmol) was dissolved in dichloromethane (80 mL) and cooled to −78 °C under an atmosphere of oxygen. Ozone was bubbled through the reaction mixture for 45 min, until the solution turned blue, after which time it was saturated with oxygen for 5 min, followed by argon for a further 5 min. Dimethyl sulfide (30 mL, 410 mmol) was added to the reaction mixture, which was allowed to stir and warm to room temperature over 16 h. The resultant solution was concentrated under reduced pressure to yield a yellow oil, dissolved in xylene (50 mL) before the addition of D-(+)-camphor sulfonic acid (624 mg, 2.69 mmol). This was stirred and heated to 110 °C for 16 h before being allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure, and purification by column chromatography (silica, eluting with petrol/ethyl acetate 90:10) afforded the title compound **14** as a yellow oil (2.52 g, 72%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.83 (3H, s), 2.09 (6H, s), 4.50 (1H, ddd, J = 20, 3.7, and 2.1 Hz), 4.97 (1H, ddd, J = 20, 2.7, and 2.1 Hz), 6.26 (1H, ddd, J = 11, 2.7, and 2.1 Hz), 7.00−7.05 (3H, m), 7.09 (1H, ddd, J = 11, 3.7, and 2.1 Hz).

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(11) Extended enolates, like pentadienyl anions, react with electrophiles at the middle carbon; see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: Chichester, 1976.

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To conclude, we have shown that the reductive alkylation/aldol ring expansion sequence is capable of producing (enantiopure) dihydropyranone building blocks in excellent yields using a readily available chiral auxiliary. This methodology has been used without any problems on a multigram scale. These compounds have a range of functionality suitable for further derivatization and preliminary experiments have shown that functionalized sugar templates can be easily prepared. We expect this methodology to have potential in the synthesis of biologically active compounds, and further work is in progress.

Acknowledgment. We thank the EPSRC and the James Black Foundation for funding this project and Pfizer for unrestricted financial support.

Supporting Information Available: Detailed spectroscopic data for new compounds and representative experimental procedures, plus X-ray data for compounds **5** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0263595