ORGANIC LETTERS

2006
Vol. 8, No. 18
4075−4078

Diastereoselective [4 + 4]-Photocycloaddition Reactions of Pyran-2-ones: Rapid Access to Functionalized 5–8–5 Skeletons

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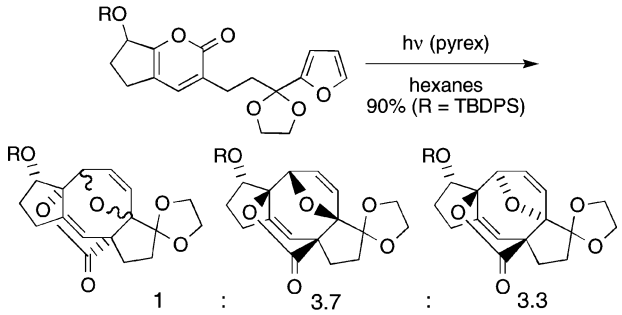
Received June 27, 2006

ABSTRACT



Fused bicyclic pyran-2-ones with pendant furan side chains and an oxygenated stereogenic center adjacent to the pyranone ring oxygen were prepared via $FeCl_3$-catalyzed Michael addition. Irradiation furnished the corresponding lactone-bridged tricyclic [4 + 4]-cycloadducts with good facial selectivity. Surprisingly, the major isomer resulted from approach of the furan from the same face as the protected alcohol.

Cyclooctane rings are found in a wide variety of biologically significant and structurally complex natural products. The well-documented challenges associated with formation of eight-membered rings[1] have prompted the development of a number of elegant strategies toward this ring system.[2] Cycloaddition approaches have attracted considerable attention since they furnish the target structure in a highly convergent fashion from relatively simple, unsaturated precursors. Several important transition-metal-catalyzed methods have been described, including Ni-mediated 4 + 4 cycloaddition of 1,3-dienes[3] and rhodium-catalyzed three-component coupling processes.[4] Concerted [4 + 3]-cycloadditions of cyclopentenyl cations and 1,2-dienes function as formal [4 + 4]-cycloadditions, providing keto-bridged cyclooctenes[5] whose one-carbon bridge can then be synthetically modified en route to various cyclooctane-containing structures.[6] Photochemical [4 + 4]-cycloadditions have also proven to be effective in assembling cyclooctanoids.[7] In this regard, we have previously examined the crossed [4 +

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(1) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.
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(3) (a) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suárez-Sobrino, A.; Vågberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908−4909. For other recent examples of transition metal mediated 4 + 4 processes, see: (b) Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, 951−953. (c) Takahashi, T.; Sun, W.-H.; Liu, Y.; Nakajima, K.; Kotora, M. *Organometallics* **1998**, *17*, 3841−3843.
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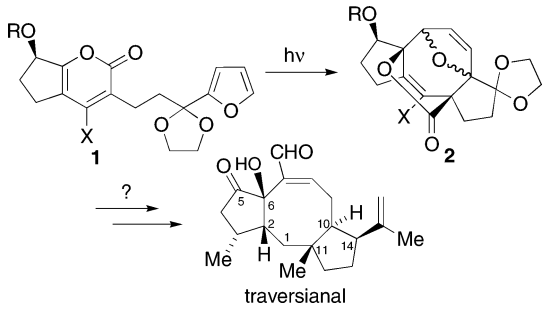
10.1021/ol061576h CCC: $33.50
Published on Web 08/11/2006

4]-photocycloaddition reactions of pyran-2-ones with pendant furan traps.[8,9] We were especially interested in the use of this methodology to the construction of tricyclic intermediates suitable for use in the synthesis of various members of the fusicoccin family of diterpenoid fungal products,[10] including traversianal[11] (Scheme 1). Here, we describe its successful

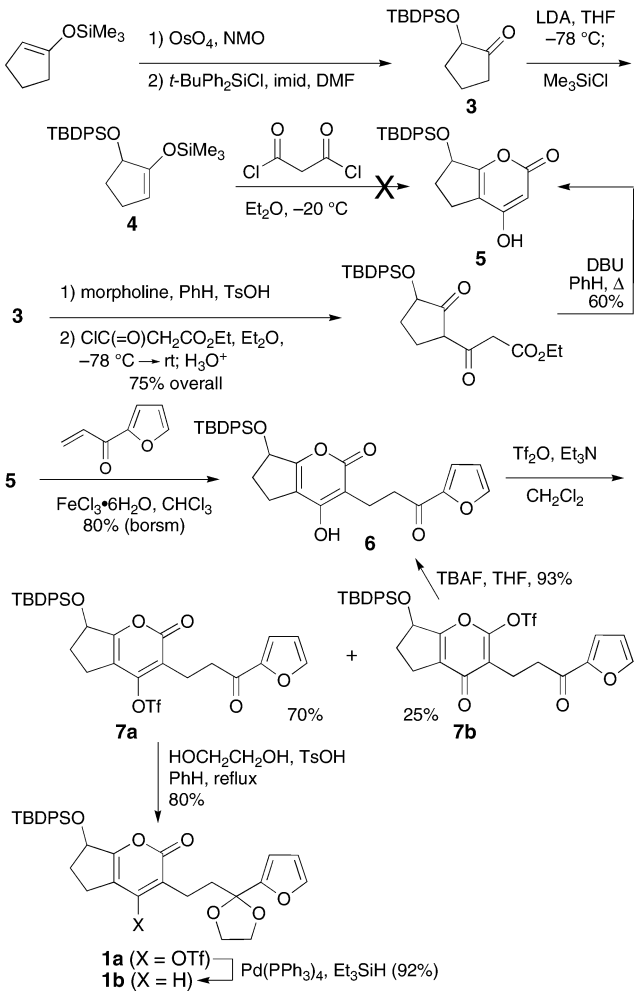
Scheme 1



application in a concise stereocontrolled route to functionalized 5−8−5 tricyclic skeletons in which the key step proceeds with remarkable selectivity in favor of approach by the furan trap from the sterically more demanding face of the bicyclic pyran-2-one.

The synthetic plan called for a fused bicyclic pyran-2-one such as **1**, in which the cyclopentene stereogenic center at the carbon corresponding to C-5[12] would control the approach of the furan in the cycloaddition to give **2**. The bridging lactone would serve as a precursor to the cis-disposed angular hydroxyl at C-6 and the methyl at C-11, while the stereochemical control element at C-5 would be oxidized to the necessary ketone. Hydrogenation of the cyclooctadiene would also be required, with selective delivery to the C-1/C-2 alkene from the top face. A protected ketone in the 3-carbon tether could provide a suitable handle for reductive opening of the furan bridge, as well as introduction of the isopropenyl group at C-14. The question of endo vs exo diastereomers in the [4 + 4]-cycloaddition

Scheme 2



could be ignored, since C-7 would become an sp^2 center and C-10 would be subject to epimerization during reductive cleavage of the bridging ether.[13] Thus, initial efforts focused on the efficient preparation of compound **1**.

We previously prepared a similar substrate via Pd(0)-catalyzed allylation of a bicyclic hydroxypyrone.[8b] However, incorporation of the C-5 alcohol and C-14 ketal required a modified route (Scheme 2). 2-Silyloxycyclopentanone **3** was prepared via dihydroxylation of trimethylsilyloxycyclopentene followed by protection of the secondary alcohol, and then converted to silyl enol ether **4**. To evaluate the feasibility

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(8) (a) West, F. G.; Chase, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 3794−3795. (b) Chase, C. E.; Bender, J. A.; West, F. G. *Synlett* **1996**, 1173−1175.

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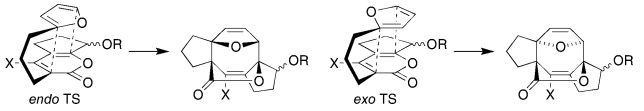
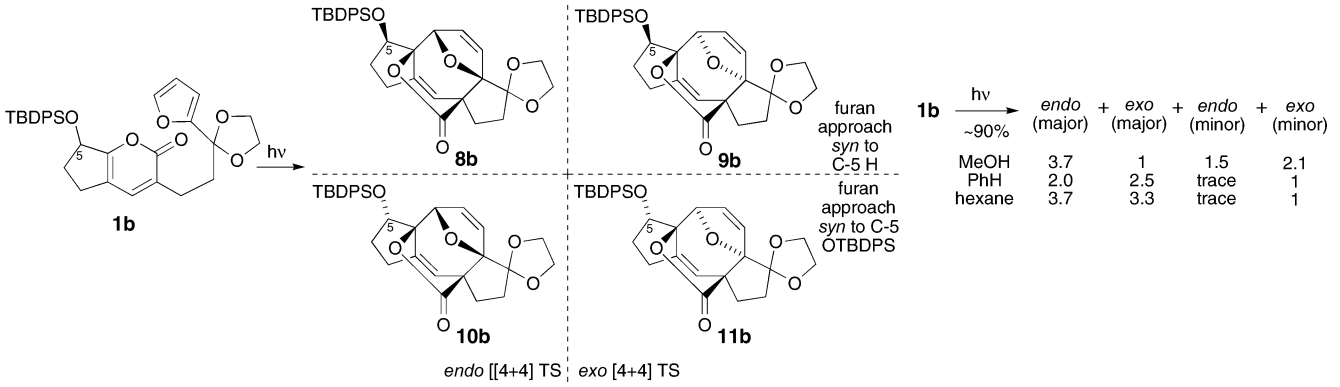
(11) (a) Stoessl, A.; Rock., G. L.; Stothers, J. B.; Zimmer, R. C. *Can. J. Chem.* **1988**, *66*, 1084−1090. (b) Stoessl, A.; Cole, R. J.; Abramowski, Z.; Lester, H. H.; Towers, G. H. N. *Mycopathologia* **1989**, *106*, 41−46.

(12) The fusicoccane/cotylen numbering system is used. See Scheme 1.

(13) Endo and exo in this context refer to the relative orientations of the two diene reactants in the [4 + 4]-cycloaddition transition state. The endo transition state places the furan C-3 and C-4 over the internal carbons of the pyran-2-one diene system, leading to a product in which the lactone and ether bridges are cis in the newly formed cyclooctadiene. The *exo* transition state places the furan C-3 and C-4 over the lactone moiety, leading to a product with the lactone and ether bridges trans disposed on the cyclooctadiene. For substrates such as **1** possessing a preexisting stereocenter, two endo and two exo products are possible, corresponding to approach of the furan from the same or the opposite face as the OR group.



Scheme 3

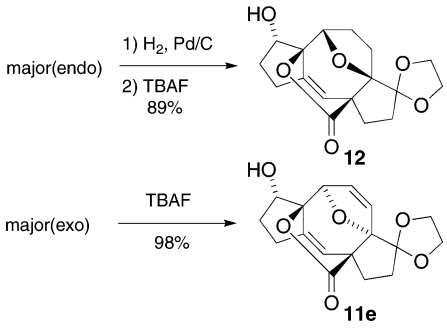


of this approach, the substrate was prepared as a racemate, but optically pure material is available by various methods.[14] Attempted cyclocondensation of malonyl dichloride with **4** failed to yield the desired pyran-2-one **5**, despite its close structural analogy to other silyl enol ethers that successfully undergo this process.[15,16] Instead, **3** was converted to its morpholine enamine and treated with methyl malonyl chloride, and the intermediate diketoester was cyclized by stirring with DBU to give **5**. Compound **5** underwent iron-(III) choride catalyzed Michael addtion to acryloyl furan to give **6**.[17] In anticipation of the eventual need for deoxygenation at C-1 of the tricyclic skeleton, the hydroxypyrone was converted to the triflate **7a**.[18] Minor amounts of the isomeric pyran-4-one **7b** formed in this reaction could be recycled by conversion to **6** upon treatment with tetrabutylammonium fluoride. Ketalization of the ketone in the tether then furnished **1a**. Reductive removal of the triflate (Pd^0/Et_3SiH)[19] gave deoxygenated substrate **1b**.

With these substrates in hand, we set out to examine their photochemical behavior, using the standard conditions developed for related pyran-2-one substrates.[8b] Substrates were anticipated to provide four stereoisomers: endo and exo cycloadducts **8** and **9** resulting from approach of the furan opposite to the C-5 OR group and endo and exo adducts **10** and **11** resulting from furan delivery from the same face as the OR group (Scheme 3). Initial experiments with substrate **1b** revealed relatively poor facial selectivity in methanol: two pairs of apparent endo/exo isomers were isolated in a disappointing 4:3 ratio, albeit in good combined yield. The identity of the major pair of isomers was assumed to be **8b** and **9b**, based on predicted approach of the furan from the sterically less demanding face. Irradiation in nonpolar solvents led to increased facial selectivity, and hexane was used in subsequent experiments due to the greater solubility of the photosubstrates **1** in this solvent as compared with benzene.

Given the improved selectivity, crystalline derivatives of the two major isomers were sought in order to make unequivocal assignments. In the event, two suitably crystalline alcohols were obtained and their structures determined by X-ray diffraction (Scheme 4). To our surprise, these

Scheme 4



structures proved to be tricyclic compounds **12** and **11e**, indicating that the major isomers from irradiation of **1b** were **10b** and **11b** and that the *dominant* pathway involves approach of the furan from the same face as the bulky OTBDPS group![20]

This unexpected diastereoselectivity prompted us to examine the effects of the alcohol protecting group R and ring substituent X (Table 1). Substrates **1c**−**e** were prepared by deprotection of **1b** (TBAF) and (for **1c**,**d**) derivatization with the appropriate reagents (TBDMSCl/imidazole or Ac_2O/pyridine/DMAP). Following irradiation, the photocycloadducts in each case were deprotected and correlated with **8e**, **9e**, **10e**, and **11e**.

(14) (a) Lee, L. G.; Whitesides, G. M. *J. Org. Chem.* **1986**, *51*, 25−36. (b) Easwar, S.; Desai, S. B.; Narshinha, P.; Ganesh, K. N. *Tetrahedron: Asymmetry* **2002**, *13*, 1367−1371. (c) Tanyeli, C.; Turkut, E.; Mecidoglu Akhmedov, I. *Tetrahedron: Asymmetry* **2004**, *15*, 1729−1733.

(15) Effenberger, F.; Ziegler, T.; Schöwalder, K.; Kesmarsky, T.; Bauer, B. *Chem. Ber.* **1986**, *119*, 3394−3404.

(16) The corresponding TBS and MOM ethers also failed to react with malonyl dichloride. Thus, although sterics may play a role, we believe that inductive deactivation of the silyl enol ether is the principal reason for the negative outcome of this annulation.

(17) Jens, C. *Synlett* **2001**, 723−732.

(18) We anticipated removal of the triflate could take place either before or after photocycloaddition. The latter approach would rely on our previous observation that hydrogenolysis of vinyl triflates in [4 + 4]-cycloadducts of 4-trifloxypyran-2-ones occurs efficiently under conditions for hydrogenation of the cyclooctadiene (see ref 8b).

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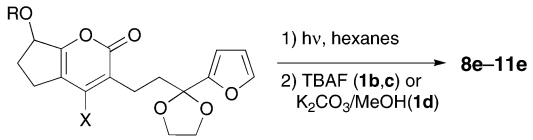
(20) X-ray data in CIF format can be found in the Supporting Information.

Table 1. [4 + 4]-Photocycloaddition Reactions of **1a**−**e**[a]



1a (R = SiO(*t*-Bu)Ph_2, X = OTf)
1b (R = SiO(*t*-Bu)Ph_2, X = H)
1c (R = SiO(*t*-Bu)Me_2, X = H)
1d (R = Ac, X = H)
1e (R = H, X = H)

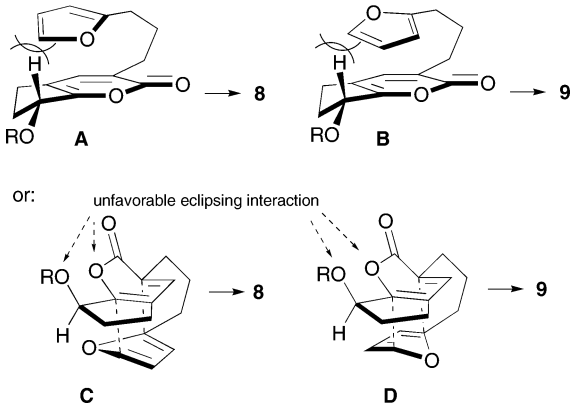
entry	substrate	overall yield[a] (%)	ratio **8/9/10/11**	facial selectivity (**10** + **11**)/(**8** + **9**)
1	**1b**	90	0[c]:1.0:3.7:3.3	7.0:1
2	**1c**	75	1.0:2.4:10.0:9.4	5.7:1
3	**1d**	70	1.0:1.9:3.1:3.8	2.3:1
4	**1e**	84	1.0:2.0:4.0:3.5	2.5:1
5	**1a**	95	1.5:1.0:8.3:2.7	4.4:1

[a] Photoreactions were carried out at ice−water bath temperature in hexane (0.1 M) under N_2 atmosphere using a Hanovia 450 W medium-pressure Hg vapor lamp. Irradiation was continued until complete consumption of starting material (typically 0.5−3 h). [b] Yields based on isolated material after chromatography. Ratios were determined by integration of the isolated trisubstituted alkene protons of **8e**−**11e** following deprotection step. [c] In some runs, trace amounts of **8a** were isolated.

In all cases, overall photocycloaddition yields were good, and isomers **10** and **11** were the major products; however, as the size of the R groups decreased, the relative amounts of the minor isomers increased (entries 1−4). Triflate-substituted compound **1a** gave comparable results (entry 5). In this case, the major photoproducts were correlated with the **10b** and **11b** by reductive removal of the triflate (Pd-(PPh_3)$_4$/Bu_3SnH).

Our assumption that isomers **8** and **9** would predominate was based upon a steric approach control selectivity argument. For **1b**, it was expected that the bulky TBDPS group would inhibit delivery of the furan from that face. Clearly, other factors are dominant in the cycloaddition transition state. It is possible that the silyl ether assumes a pseudoequatorial situation on the cyclopentene ring, with approach from the opposite face hindered by the pseudoaxial hydrogen atom (conformers **A** and **B**, Scheme 5). Alternatively, a product development control argument may explain both the overall facial selectivity and the increased selectivity seen with larger R groups. Approach of the furan from the opposite face as the OR group entails movement of the lactone bridge toward an eclipsing interaction with OR as bonding proceeds (conformers **C** and **D**), whereas approach from the same face

Scheme 5



causes the lactone to move away from OR and toward the methine hydrogen. Further examples are under study in order to better understand the origins of this effect; however, from the standpoint of a stereocontrolled route to traversianal and related compounds, this surprising result does not abrogate the original synthetic plan. The site of the original stereochemical control element will ultimately become an sp^2 center, although the enantiomer of the initially proposed substrate will be required.

We have described a novel strategy for the stereoselective construction of functionalized 5−8−5 tricyclic systems using the crossed intramolecular [4 + 4]-photocycloaddition of pyran-2-ones. By this route, complex polycycles that are potentially suitable intermediates for the synthesis of traversianal and members of the fusicoccin class of fungal metabolites are available in 7−9 steps from 2-siloxycyclopentanone **3a**. By inclusion of a preexisting stereocenter on a cyclopentene ring fused to the pyran-2-one, facial selectivities of up to 7:1 are obtained. Notably, the major isomers arise from approach of the furan trap from the *same* face as the bulky substituent. Further studies of this interesting example of stereocontrol, and progress toward various natural product targets, will be reported in due course.

Acknowledgment. We thank NSERC for support of this work.

Supporting Information Available: Experimental procedures and spectral data for all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061576H