ORGANIC LETTERS

2008
Vol. 10, No. 24
5553−5556

Consecutive Alkene Cross-Metathesis/ Oxonium Ylide Formation−Rearrangement: Synthesis of the Anti-HIV Agent Hyperolactone C

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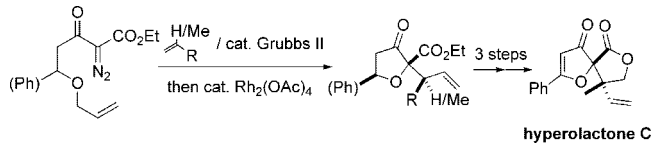
Received October 13, 2008

ABSTRACT

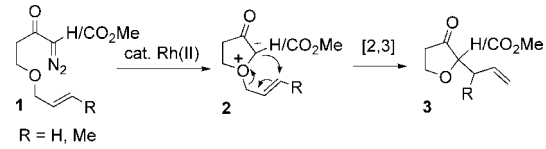


α-Diazo-β-ketoesters bearing allylic ether functionality undergo highly stereoselective Ru-carbene-catalyzed alkene cross-metathesis followed by $Rh_2(OAc)_4$-catalyzed oxonium ylide formation/[2,3] sigmatropic rearrangement in a one-flask operation and in a highly diastereoselective manner. The methodology has been demonstrated in a concise synthesis of the anti-HIV agent hyperolactone C.

We previously demonstrated the coupling of two different, synthetically important transition-metal-catalyzed carbene transformations (alkene cross-metathesis[1] and diazocarbonyl-derived tandem carbonyl ylide formation−intramolecular 1,3-dipolar cycloaddition)[2] in a one-pot operation to access complex oxapolycycles.[3] This process allowed rapid assembly of complex molecular structures and suggested further opportunities for combining one-pot alkene cross-metathesis with other transformations of diazo compounds.

Oxonium ylides (e.g., **2**, Scheme 1) are reactive intermediates with a postively charged oxygen atom bonded to a carbon possessing an unshared pair of electrons. One convenient approach to oxonium ylides involves the interaction of a diazocarbonyl-derived metallocarbene with an unshared pair of electrons from an ethereal oxygen (e.g., **1**→**2**).[2,4] Pirrung[5] and Johnson[6] independently established the synthetic utility of tandem oxonium ylide formation−rearrangement. They explored the intramolecular generation of diazocarbonyl-derived unsaturated oxonium ylides **2** via Rh(II) and Cu(II) carbenoids and their subsequent [2,3] sigmatropic rearrangement to give, for example, dihydrofuranones **3** (Scheme 1).[7]

Scheme 1. Oxonium Ylide Formation−Rearrangement



(1) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003.

(2) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons: New York, 1998.

(3) (a) Hodgson, D. M.; Angrish, D.; Labande, A. H. *Chem. Commun.* **2006**, 627–628. (b) Hodgson, D. M.; Angrish, D. *Adv. Synth. Catal.* **2006**, *348*, 2509–2514.

(4) Clark, J. S. *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Oxford University Press: Oxford, 2002; Chapter 1.

(5) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060–6062.

(6) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062–6063.

10.1021/ol802334y CCC: $40.75
Published on Web 11/17/2008

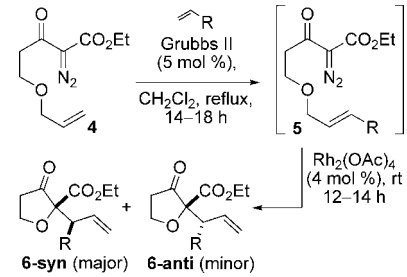
The scope of this chemistry has subsequently been examined toward the synthesis of several natural products.[8] Rapid access to varied 2-substituted dihydrofuranones **3** would be facilitated by late-stage diversification of the unsaturation in a rearrangement precursor **1** and would also allow a straightforward analysis of the effect of alkene substitution on the rearrangement chemistry. Herein, we describe one-pot alkene cross-metathesis/oxonium ylide formation and highly diastereoselective [2,3] sigmatropic rearrangement to access dihydrofuranones and application of the methodology in a synthesis of hyperolactone C.

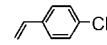
First, we examined the viability of allylic ether functionality to undergo cross-metathesis in the presence of a tethered diazocarbonyl group. Cross-metathesis of α-diazo-β-ketoester **4**[5,9] with olefins (5−10 equiv) was carried out using Grubbs II catalyst (5 mol %) in CH_2Cl_2 at reflux for 14−18 h (Table 1). The substituted alkenes **5** were obtained in moderate to excellent yields and generally with high stereoselectivity. Cross-metathesis with 2-methyl-2-butene proceeded smoothly to give the prenyl ether in excellent yield (entry 1). Vinylcyclohexane underwent efficient cross-metathesis (89%), but the sterically hindered 3,3-dimethyl-1-butene gave only 50% cross-metathesis (entries 2 and 3). Styrene and substituted styrenes were also found to be less efficient partners during cross-metathesis with allyl ether-tethered α-diazo-β-ketoester **4** (entries 4−6), compared to the diazo precursor to tandem carbonyl ylide formation−1,3-dipolar cycloaddition;[3] however, the reaction proceeded with high stereoselectivity to give predominantly *E*-isomers. α,β-Unsaturated esters were quite efficient partners and gave disubstituted α,β-unsaturated esters with high stereoselectivity (entries 7 and 8).

Encouraged by the ability of **4** to undergo stereoselective cross-metathesis in the presence of diazo and allylic ether functionalities, we examined one-pot cross-metathesis/oxonium ylide formation−rearrangement. The sequence was carried out using Grubbs II catalyst (5 mol %) with α-diazo-β-ketoester **4** and metathesis partner (5−10 equiv) in CH_2Cl_2 at reflux for 14−20 h, followed by addition of $Rh_2(OAc)_4$ (4 mol %) at room temperature (TLC monitoring, ∼12−14 h). The methodology was first tested with 2-methyl-2-butene, as a closely related prenyl ether had already been shown by Hashimoto and co-workers to undergo a tandem oxonium ylide formation/[2,3] sigmatropic rearrangement.[10] In the event, in situ generated prenyl ether **5a** gave dihydrofuranone **6a** in 87% yield in the one-pot process (compared to 73% yield obtained with the corresponding methyl ester by Hashimoto[10] for the ylide transformation only) (Table 1, entry 1). Vinylcyclohexane also worked efficiently in the one-pot procedure to give the dihydrofuranone **6b** in good yield (entry 2) and with high diastereoselectivity (90:10). However, sterically hindered 3,3-dimethyl-1-butene gave the desired dihydrofuranone **6c** in only modest yield (49%), but with high diastereoselectivity (94:6) (entry 3); no change in dr was observed when this Rh-catalyzed ylide rearrangement was carried out at reflux (dr = 93.5:6.5, with 54% isolated one-pot yield for **6c**), suggesting that the dr of rearrangement is relatively independent of the reaction temperature. Styrene and substituted styrenes also gave the dihydrofuranones **6d**−**f** in moderate yields (51−66%), but with high levels of diastereoselectivity (entries 4−6). The modest yield during the one-pot procedure for these olefins likely reflects cross-metathesis efficiency with α-diazo-β-ketoester **4** (entries 3−6). The influence of ester functionality on the diastereoselectivity of the rearrangement was then studied. Esters showed excellent diastereoselectivity and very good yields during the process. No effect of sterics of the ester was observed. The methyl ester gave >99:1 dr (entry 7), and a *tert*-butyl ester gave 98:2 dr (entry 8).

Complete allylic transposition in the above reactions indicates that from oxonium ylide **2** a pericyclic ([2,3] sigmatropic rearrangement) pathway is likely preferred over one involving C−O cleavage−recombination.[2,4] In most cases, diastereoselectivity arising from the ylide rearrange-

Table 1. Cross-Metathesis and Oxonium Ylide Formation−Rearrangement Using Diazoester **4**



entry	metathesis partner	cross-metathesis % (*E*:*Z*)[a]	yield % in one-pot; (dr)[a]
1		**5a** 82 (−)	**6a** 87 (−)
2		**5b** 89 (90:10)	**6b** 79 (90:10)
3		**5c** 50 (>99:1)	**6c** 49 (94:6)
4		**5d** 47 (94:6)	**6d** 66 (94:6)
5		**5e** 65 (98:2)	**6e** 63 (98:2)[b]
6		**5f** 54 (97:3)	**6f** 51 (93:7)
7		**5g** 86 (95:5)	**6g** 81 (>99:1)
8		**5h** 78 (>99:1)	**6h** 82 (98:2)

[a] Determined by ^{1}H NMR. [b] Determined by GC−MS.

(7) For [2,3] sigmatropic rearrangement of oxonium ylides formed under $Rh_2(OAc)_4$ catalysis via in situ generated iodonium ylides, see: Murphy, G. K.; West, F. G. *Org. Lett.* **2006**, *8*, 4359–4361.

(8) (a) Pirrung, M. P.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561–8562. (b) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773–1776. (c) Yakura, T.; Muramatsu, W.; Uenishi, J. *Chem. Pharm. Bull.* **2005**, *53*, 989–994. (d) Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron* **2005**, *62*, 73–78. (e) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 437–440. (f) Clark, J. S.; Baxter, C. A.; Dossetter, A. G.; Poigny, S.; Castro, J. L.; Wittingham, W. G. *J. Org. Chem.* **2008**, *73*, 1040–1055.

(9) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983–5986.

(10) Kitagaki, S.; Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361–6364.

ment matched the stereoselectivity seen during cross-metathesis, suggesting one transition-state orientation is strongly favored (see below). However, a slight erosion of diastereoselectivity was observed for the olefins bearing *tert*-butyl and *p*-chlorophenyl groups (entries 3 and 6). The relative stereochemistry of the major diastereomer of **6f** was supported by X-ray crystallographic analysis (Figure 1),[11] and the rest of the major dihydrofuranone products **6** were assigned by analogy.

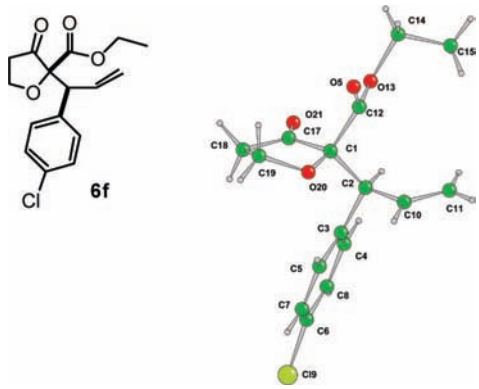
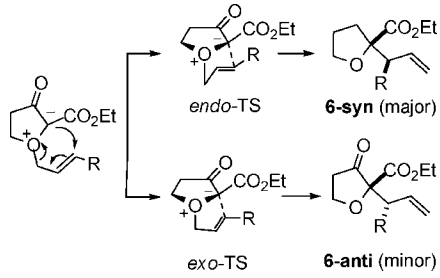


Figure 1. X-ray structure of dihydrofuranone **6f-syn**.[11]

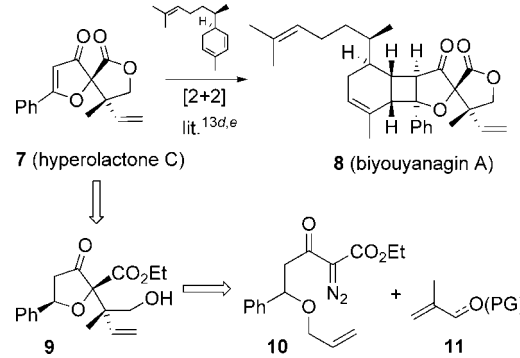
[2,3] Sigmatropic rearrangement of the putative oxonium ylide intermediates in the above chemistry can in principle proceed via *exo* and/or *endo* transition states (TSs) (Scheme 2). If rearrangement proceeds through an *endo*-TS, **6-syn** will be obtained; however, if the rearrangement proceeds through an *exo*-TS, diastereomer **6-anti** will be formed. The crystal structure for **6f** suggests that the ylide rearrangement proceeds preferentially via an *endo*-TS. Although the origin of this stereoselectivity is not currently known, our observations are in accordance with results obtained by Clark and co-workers concerning oxonium ylide rearrangement of α-diazoketones.[8b]

Scheme 2. Rearrangement Transition States



Hyperolactone C (**7**)[12] is a structurally interesting spirolactone with adjacent quaternary stereocenters. It is a known precursor of the anti-HIV agent biyouyanagin A (**8**)[12d] and is of significant current interest given that the biological activity of biyouyanagin A has recently been reported to reside in the hyperolactone C structural domain.[12e] The structural complexity of hyperolactone C and potential as a new lead in anti-HIV research combine to make it an attractive target, which we considered could be accessed by an extension of the above metathesis−oxonium ylide chemistry (Scheme 3). Specifically, we envisaged hyperolactone C as arising from spirolactonization and dehydrogenation of dihydrofuranone **9**. Dihydrofuranone **9** was anticipated to originate from *E*-selective cross-metathesis of unsaturated α-diazo-*β*-ketoester **10** and an appropriate partner alkene **11**, followed by oxonium ylide generation and *endo*-selective [2,3] sigmatropic rearrangement on the face of the ylide away from the phenyl group.

Scheme 3. Strategy to Hyperolactone C



Oxonium ylide precursor **10** was synthesized by a Lewis acid catalyzed Mukaiyama-type aldol condensation between (bis(allyloxy)methyl)benzene[13] and the silyl enol ether of commercially available ethyl diazoacetoacetate (**12**), following a modified literature procedure (Scheme 4).[14]

As a model study, the α-diazo-*β*-ketoester **10** was subjected to $Rh_2(OAc)_4$-catalyzed oxonium ylide formation−rearrangement. The corresponding dihydrofuranone **13** was obtained in 99% yield with high diastereoselectivity (91:9, stereochemistry assigned by NOE studies).[11] The cross-metathesis of allyl ether **10** with *gem*-disubstituted olefins **11** containing requisite oxygen functionality proved challenging, with benzoyl- or trityl-protected methallyl alcohol proceeding with modest *E*:*Z* selectivity (63:37 and 83:17, respectively) and in low yields (22% and 6%, respectively). However, cross-metathesis with 2-methyl-2-butene proceeded well to give the corresponding prenyl ether in 81% yield

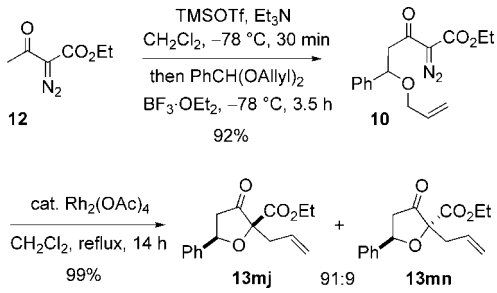
(11) See the Supporting Information for further details.

(12) For isolation and structure elucidation, see: (a) Aramaki, Y.; Chiba, K.; Tada, M. *Phytochemistry* **1995**, *38*, 1419–1421. For previous syntheses, see: (b) Ueki, T.; Doe, M.; Tanaka, R.; Morimoto, Y.; Yoshihara, K.; Kinoshita, T. *J. Heterocycl. Chem.* **2001**, *38*, 165–172. (c) Kraus, G. A.; Wei, J. *J. Nat. Prod.* **2004**, *67*, 1039–1040. (d) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4708–4711. (e) Nicolaou, K. C.; Wu, T. R.; Sarlah, D.; Shaw, D. M.; Rowcliffe, E.; Burton, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 11114–11121.

(13) Brogan, J. B.; Richard, J. E.; Zercher, C. K. *Synth. Commun.* **1995**, *25*, 587–593.

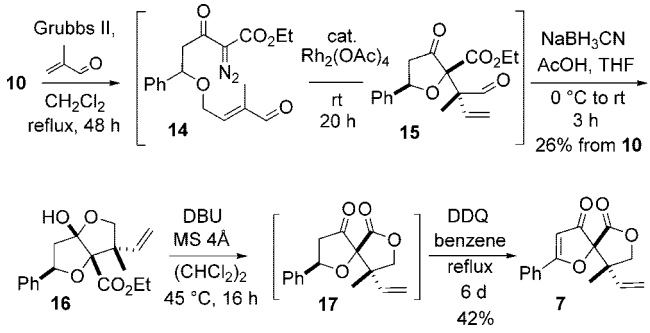
(14) Calter, M. A.; Sugathapala, P. M. *Tetrahedron Lett.* **1998**, *39*, 8813–8816.

Scheme 4. Dihydrofuranone Formation from **10**



[which smoothly underwent ylide formation−rearrangement in 75% yield, but with erosion of diastereoselectivity (65:35) compared to allyl ether **10**],[11] implying that the low metathesis yields with the above *gem*-disubstituted oxygenated olefins is not due to the phenyl group present in **10**. No cross-metathesis was observed with *tert*-butyl methacrylate, but methacrolein proved encouraging, giving only the *E*-enal **14**, albeit in 21% yield (Scheme 5).

Scheme 5. Hyperolactone C Synthesis



Other metathesis catalysts were less effective in the latter reaction. Progressing enal **14** in the oxonium ylide formation−rearrangement gave unstable aldehyde **15**, best reduced using $NaBH_3CN$ to a mixture of fused hemiketals in 69% yield over two steps and in 80:13:4:3 diastereoselectivity (determined by ^1H NMR) in favor of the desired isomer **16** (stereochemistry assigned by NOE studies),[11] which was cleanly isolated from the mixture. From unsaturated α-diazo-β-ketoester **10**, one-pot cross-metathesis/[2,3] sigmatropic rearrangement and reduction of the resulting crude material gave hemiketal **16** in 26% yield. Spirolactonization of the hemiketal **16** using DBU[15] gave crude spirolactone **17** which was directly dehydrogenated using DDQ[16] giving hyperolactone C (**7**) (42% over two steps), with data consistent with the literature.[11,12]

In summary, we have demonstrated the ability of α-diazo-β-ketoesters bearing an allylic ether tether to undergo stereoselective cross-metathesis, thus expanding the range of functional group compatibility of Grubbs' catalyst to such diazo compounds. The α-diazo-β-ketoesters have also been shown to undergo one-pot cross-metathesis/[2,3] sigmatropic rearrangement via oxonium ylides to access dihydrofuranones diastereoselectively; the latter further demonstrating the compatibility of Ru and Rh catalysis in a one-pot procedure. Finally, a synthesis of the anti-HIV agent hyperolactone C has been accomplished using cross-metathesis followed by a diastereoselective tandem oxonium ylide formation and [2,3] sigmatropic rearrangement sequence as key transformations.

Acknowledgment. We thank the University of Oxford for a full Clarendon Fund bursary award (to D.A.) and the following people from Oxford (Chemistry Research Laboratory): Dr. B. Odell (NOE studies), R. Procter (mass spectra), and Dr. D. Watkin and R. Thomas (X-ray crystallographic analysis).

Supporting Information Available: Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802334Y

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