Pergamon

Tetrahedron Letters 39 (1998) 4651–4654

TETRAHEDRON LETTERS

RING-CLOSING METATHESIS STRATEGY TO UNSATURATED γ- AND δ-LACTONES: SYNTHESIS OF HYDROXYETHYLENE ISOSTERE FOR PROTEASE INHIBITORS

Arun K. Ghosh,* John Cappiello and Dongwoo Shin

Department of Chemistry, University of Illinois at Chicago,
845 West Taylor Street, Chicago, Illinois 60607.

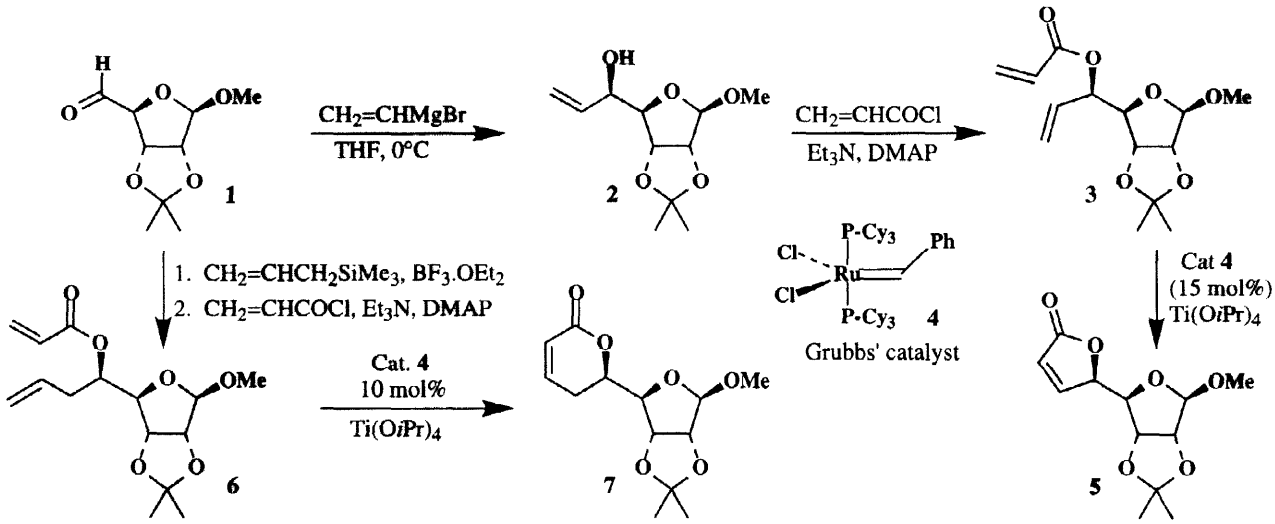
Received 23 March 1998; revised 15 April 1998; accepted 16 April 1998

Abstract: Ring-closing olefin metathesis of acrylates derived from allylic and homo allylic alcohols in the presence of the Grubbs' catalyst (10-15 mol%) and titanium isopropoxide (0.3-3 equiv) provided ready access to α, β-unsaturated γ- and δ-lactones and an important dipeptide isostere intermediate.

Transition metal catalyzed ring-closing olefin metathesis has been the subject of much attention in recent years.[1] The development of ruthenium carbene complexes by Grubbs and coworkers is particularly notable because of the remarkable functional group tolerance, operational simplicity and ready availability.[2] The immense synthetic potential of this catalytic process is already evident in numerous recent syntheses of biologically important natural products with diverse functionalities as well as varied ring sizes.[3,4] We have recently reported the synthesis of novel macrocyclic urethanes utilizing a ring closing strategy.[5] In our continuing efforts in the design and synthesis of nonpeptidyl protease inhibitors, we required a convenient synthetic route to structurally diverse unsaturated γ- and δ-lactones. The ring-closing metathesis of acrylates derived from allylic and homoallylic alcohols appeared conveniently poised to provide such five and six-membered unsaturated lactones. While the strategy seems appealing, one possible caveat is the formation of unproductive stable six and seven-membered metal chelates with the ester carbonyl and the resulting carbene species which may hinder olefin metathesis. However, Fürstner and Langemann have shown that the presence of titanium isopropoxide destabilizes such unproductive complexes and results in effective cyclization.[6] Herein, we report the ring-closing metathesis of acrylates of allylic and homo allylic alcohols with the Grubbs' catalyst (10-15 mol%) in the presence of titanium isopropoxide (0.3-3 equiv). This method provides convenient access to α, β–unsaturated γ- and δ-lactones in good to excellent yields. The amino acid derived γ-lactone can be converted to the hydroxyethylene isostere, a key intermediate for potent and selective HIV protease inhibitors.[7]

As shown in Scheme 1, the reaction of aldehyde **1** with vinylmagnesium bromide in THF at 0° to 23° C for 3 h afforded the allyl alcohol **2** as a mixture (3:1) of diastereomers (70% yield).[8] Reaction of **2** with acryloyl chloride (1.2 equiv) and Et_3N (3 equiv) in the presence of a catalytic amount of DMAP in CH_2Cl_2 provided the acrylate ester **3** (65%). Reaction of aldehyde **1** with allyltrimethylsilane in the presence of $BF_3.OEt_2$ at -78°C and subsequent acylation of the resulting homo allylic alcohol afforded the acrylate ester **6** as a single isomer.[8] The threo alcohol in entry 3 (Table 1) was prepared by reaction of BOC-phenylalaninal with excess vinyl zinc chloride in THF at

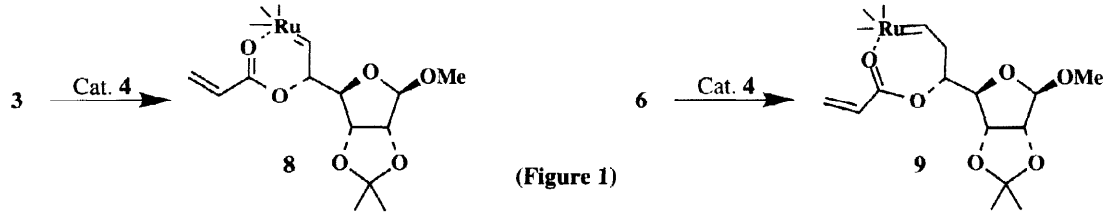
0040-4039/98/$19.00
PII: S0040-4039(98)00887-9



Scheme 1

-40° C for 2 h (65%).[9] Treatment of BOC-phenylalaninal with $SnCl_4$ (2 equiv) at -78° C in CH_2Cl_2 followed by dropwise addition of allyltributyltin afforded the threo homo allylic alcohol for entry 4.[10] Various alcohols for entries 5-10 were prepared by addition of vinyl and allylmagnesium bromides to the respective carbonyl derivative at -20° to 0°C (65-75%). The resulting allylic or homo allylic alcohols were converted to their respective acrylate esters as described above.

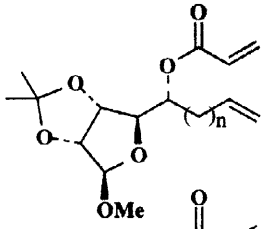
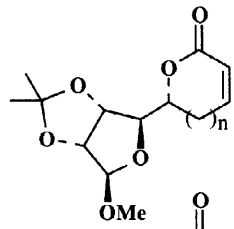
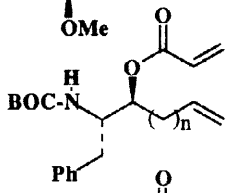
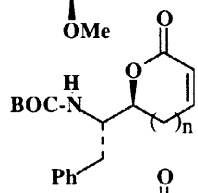
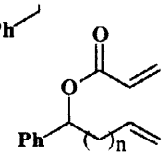
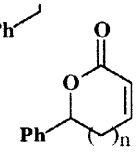
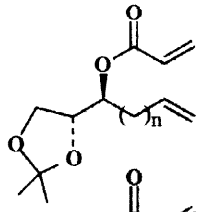
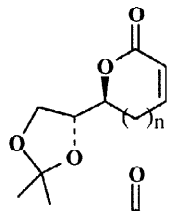
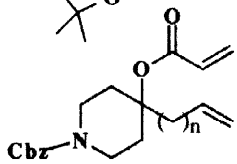
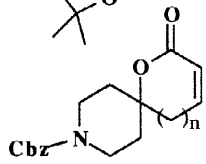
Initial exposure of acrylate ester **3** to commercially available Grubbs' catalyst **4** (10 mol%) in CH_2Cl_2 (0.007 M solution) at 40°C for 15 h resulted in low conversion of lactone **5** (40% by ^{1}H-NMR) and a substantial amount of unreacted starting material. The reaction of acrylate ester **6** however, required 10 h for complete conversion giving the corresponding δ-lactone **7** in 88% yield. Interestingly, when the olefin metathesis of **3** was carried out utilizing Grubbs' catalyst in the presence of $Ti(OiPr)_4$ (3 equiv) at 40°C, unsaturated γ-lactone **5** was obtained in 72% yield (based on 18% recovered **3**) after 15 h. Similarly, the reaction of **6** with Grubbs' catalyst in the presence of $Ti(OiPr)_4$ (0.3 equiv) afforded the δ-lactone **7** in 94% yield with complete consumption of starting material within 2 h. The formation of six and seven-membered stable metal complexes such as **8** and **9** (Figure 1) may account for the slow conversion rate. A similar unproductive metal chelate was earlier hypothesized by Fürstner and Langemann during their synthesis of macrocyclic lactones.[6]



(Figure 1)

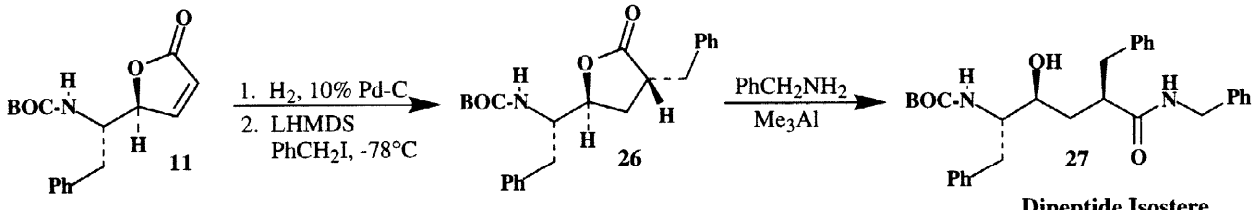
The results of olefin metathesis of various diene substrates with a range of functionalities are summarized in Table 1. The reaction in entry 3 underwent about 90% conversion whereas the reaction in entry 4 underwent complete conversion providing the corresponding δ-lactone in excellent yield. The amino acid derived γ-lactone **11** (entry 3) was converted to hydroxyethylene isostere **27** which is a versatile intermediate for the synthesis of numerous potent and selective HIV-1

Table 1. Synthesis of γ- and δ-Lactones by Ring-Closing Olefin Metathesis[a]

Entry	Diene	Cat mol% (eq LA)	γ- or δ-Lactone	Time/h	% Yield[b]
1	 **3** (n=0)	15 (2.5)	 **5** (n=0)	15	72[c,d]
2	**6** (n=1)	10 (0.3)	**7** (n=1)	2	94
3	 **10** (n=0)	10 (0.3)	 **11** (n=0)	15	82
4	**12** (n=1)	10 (0.3)	**13** (n=1)	5	84
5	 **14** (n=0)	10 (0.3)	 **15** (n=0)	10	75
6	**16** (n=1)	10 (0.3)	**17** (n=1)	10	98
7	 **18** (n=0)	10 (2.5)	 **19** (n=0)	38	49[c,d]
8	**20** (n=1)	10 (2.5)	**21** (n=1)	10	81[d]
9	 **22** (n=0)	10 (3)	 **23** (n=0)	12	54[c]
10	**24** (n=1)	10 (3)	**25** (n=1)	12	74

[a]All reactions are carried out at 40°C ; [b]Yield refers to purified product; [c]Yield based on recovered starting material (15-20%); [d]Ratio of mixture 3:1 (The structure of the major diastereomer is shown).

protease inhibitors.[7] Thus, catalytic hydrogenation of **11** over 10%Pd-C in EtOAc followed by stereoselective alkylation using lithium hexamethyldisilazide and benzyl iodide in THF at -78° C afforded the lactone **26** in 77% yield (Scheme 2).[11] The reaction of lactone **26** with benzylamine in the presence of trimethylaluminum in CH_2Cl_2 furnished the hydroxyamide **27** in 72% yield.[12]



Scheme 2

In conclusion, we have demonstrated that the ring closing olefin metathesis reaction using commercially available Grubbs' catalyst is an efficient process for the synthesis of important five and six membered lactones. Further applications of these lactones in the synthesis of novel protease inhibitors are currently in progress. The following example is representative of this procedure.

Preparation of γ-lactone 11: To a stirred solution of diene (312 mg, 0.94 mmol) in CH_2Cl_2 (94 mL) under argon was added $Ti(OiPr)_4$ (84 μl, 0.28 mmol) at 23°C. The resulting solution was refluxed at 40°C for 1 h and then Grubbs' catalyst (77.5 mg, 0.094 mmol) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at reflux for an additional 15 h. The mixture was cooled to 23°C and filtered through a pad of silica gel. Evaporation of the solvent gave a residue which was flash chromatographed over silica gel to provide the lactone **11** (201 mg, 82% yield based on recovery of 46 mg of starting diene) as a white solid (m.p. 118-120°C). ^{1}H-NMR (400 MHz): δ, 7.43 (dd, 1H, J=1.1, 5.7 Hz), 7.35-7.24 (m, 5H), 6.06 (dd, 1H, J=1.8, 5.7 Hz), 4.94 (d, 1H, J=1.3 Hz), 4.5 (d, 1H, J=8.1 Hz), 4.23-4.21 (m, 1H), 3.05-2.92 (m, 2H), 1.35 (s, 9H); ^{13}C-NMR (100 MHz): d, 173.19, 155.22, 155.05, 136.69, 129.32, 128.76, 126.98, 121.45, 82.86, 79.95, 52.50, 38.65, 28.08. IR (neat): 3328, 2978, 1753, 1688, 1524,1166 cm^{-1}; MS, m/z: 303 (M^+).

Acknowledgment: Financial support of this work by the National Institute of Health is gratefully acknowledged. The authors thank Professor George Gould for helpful discussions.

References and Notes

1. (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc.Chem.Res.* **1995**, *28*, 446; (b) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036 and references cited therein.
2. (a) Fu, G. C.; Nguyen, S. B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9858; (b) Fu, G. C.; Grubbs, R.H. *J. Am. Chem. Soc.* **1992**, *114*, 7324; (c) Fu, G. C.; Nguyen, S. B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856 and references cited therein.
3. For recent applications in the synthesis of macrocycles: (a) Yang, Y.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2801; (b) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Nikovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Glannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268; (c) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *117*, 10073; (d) Su, D.-S.; Meng, D.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 757; (e) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302; (f) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801; (g) Fürstner, A.; Langermann, K. *J. Org. Chem.* **1996**, *61*, 3942; (h) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943 and references cited therein.
4. For the synthesis of medium size rings, see: (a) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919; (b) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548; (c) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291; (d) Fu, G. C.; Nguyen, S. T. Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856 and references cited therein.
5. Ghosh, A. K. ; Hussain, K. A.; *Tetrahedron Lett.* **1998**, *39*, 1881.
6. Fürstner, A.; Langermann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.
7. (a) Ghosh, A. K.; McKee, S. P.; Thompson, W. J.; Darke, P. L.; Zugay, J. C. *J. Org. Chem.* **1993**, *58*, 1025; (b) Ghosh, A. K.; Thompson, W. J.; McKee, S. P.; Duong, T. T.; Lyle, T. A.; Cen, J. C.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 292; (c) Ashorn, P.; McQuade, T. J.; Thaisrivongs, S.; Tomasselli, A. G.; Tarply, W. G.; and Moss, B.; *Proc. Natl. Acad. Sci. USA.* **1990**, *87*, 7472 and references cited therein.
8. Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Cartey, P. A. *Tetrahedron* **1986**, *42*, 2809.
9. Thompson, W. J.; Tucker, T. J.; Schwering, J. E.; Barnes, J. L. *Tetrahedron Lett.* **1990**, *31*, 6819.
10. Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803.
11. All new compounds gave satisfactory spectroscopic and analytical results.
12. Basha, A.; Lipton, M.; and Weinreb, S. M.; *Tetrahedron Lett.* **1977**, 4171.