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

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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 Et₃N (3 equiv) in the presence of a catalytic amount of DMAP in CH₂Cl₂ provided the acrylate ester **3** (65%). Reaction of aldehyde **1** with allyltrimethylsilane in the presence of BF₃·OEt₂ 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 -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 $^1\text{H-NMR}$) 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 $\text{Ti}(\text{O}i\text{Pr})_4$ (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 $\text{Ti}(\text{O}i\text{Pr})_4$ (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

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 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

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 (84 W, 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). ¹H-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); ¹³C-NMR (100 MHz): δ, 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, 303 (M⁺).

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References and Notes

1. (a) Grubbs RH; Miller SJ; Fu GC 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 GC; Nguyen SBT; Grubbs RH J. Am. Chem. Soc 1993, 115, 9858(b)Fu GC; Grubbs RH J. Am. Chem. Soc 1992, 114, 7324(c)Fu GC; Nguyen SBT; Grubbs RH J. Am. Chem. Soc 1993, 115, 9856 and references cited therein.
3. For recent applications in the synthesis of macrocycles: Yang Y; He Y; Vourloumis D; Vallberg H; Nicolaou KC Angew. Chem. Int. Ed. Engl 1997, 36, 2801Nicolaou KC; Winssinger N; Pastor J; Nikovic S; Sarabia F; He Y; Vourloumis D; Yang Z; Li T; Glannakakou P; Hamel E Nature 1997, 387, 268 [PubMed: 9153390] Meng D; Bertinato P; Balog A; Su D-S; Kamenecka T; Sorensen EJ; Danishefsky SJ J. Am. Chem. Soc 1997, 117, 10073Su D-S; Meng D; Bertinato P; Balog A; Sorensen EJ; Danishefsky SJ; Zheng Y-H; Chou T.-c.; He L; Horwitz SB Angew. Chem. Int. Ed. Engl 1997, 36, 757xu Z; Johannes CW; Houri AF; La DS; Cogan DA; Hofilena GE; Hoveyda AH J. Am. Chem. Soc 1997, 119, 10302Balog A; Meng D; Kamenecka T; Bertinato P; Su D-S; Sorensen EJ; Danishefsky SJ Angew. Chem. Int. Ed. Engl 1996, 35, 2801Fürstner A; Langermann KJ. org. Chem 1996, 61, 3942 [PubMed: 11667264] Houri AF; xu Z; Cogan DA; Hoveyda AH J. Am. Chem. Soc 1995, 117, 2943 and references cited therein.
4. For the synthesis of medium size rings, see: Linderman RJ; Siedlecki J; O'Neill SA; Sun H J. Am. Chem. Soc 1997, 119, 6919Crimmins MT; Choy ALJ. Org. Chem 1997, 62, 7548 [PubMed: 29667840] Visser MS; Heron NM; Didiuk MT; sagal JF; Hoveyda AH J. Am. Chem. Soc 1996, 118, 4291Fu GC; Nguyen ST Grubbs RH J Am. Chem. Soc 1993, 115, 9856 and references cited therein.
5. Ghosh AK; Hussain KA; Tetrahedron Lett. 1998, 39, 1881. [PubMed: 30383041]
6. Fürstner Langermann, K. J. Am. Chem. Soc 1997, 119, 9130.
7. (a)Ghosh AK; McKee SP; Thompson WJ; Darke PL; Zugay JC J. Org. Chem 1993, 58, 1025 [PubMed: 30310240] (b)Ghosh AK; Thompson WJ; McKee SP; Duong TT; Lyle TA; cen JC; Darke PL; Zugay JA; Emini EA; Schleif WA; Huff JR; Anderson PS J. Med. Chem 1993, 36, 292 [PubMed: 8423600] (c)Ashorn P; McQuade TJ; Thaisrivongs S; Tomasselli AG; Tarply WG; and Moss B; Proc. Natl. Acad. Sci. USA 1990, 87, 7472 and references cited therein. [PubMed: 2217178]
8. Danishefsky SJ; DeNinno MP; Phillips GB; Zelle RE; Cartey PA Tetrahedron 1986, 42, 2809.
9. Thompson WJ; Tucker TJ; Schwering JE; Barnes JL Tetrahedron Lett. 1990, 31, 6819.
10. Vara Prasad JVN; Rich DH Tetrahedron Lett. 1990, 31, 1803.
11. All new compounds gave satisfactory spectroscopic and analytical results.
12. Basha A; Lipton M; and Weinreb SM; Tetrahedron Lett. 1977, 4171.

(Figure 1).

Scheme 1.

Scheme 2.

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).