Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9479–9481
Tetrahedron Letters

Synthesis of *gem*-difluoromethylenated massoialactone by ring-closing metathesis

Zheng-Wei You,[a] Yun-Yun Wu[a] and Feng-Ling Qing[a,b,*]

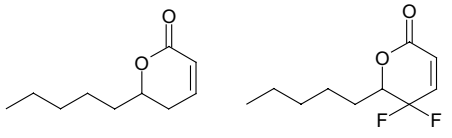
[a]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*
[b]*College of Chemistry and Chemical Engineering, Donghua University, 1882 West Yanan Lu, Shanghai 200051, China*

Received 30 July 2004; revised 28 September 2004; accepted 30 September 2004
Available online 5 November 2004

Abstract—4,4-Difluoromassoialactone has been synthesized for the first time via a very short sequence, where the ring-closing metathesis (RCM) was employed as a key step. The efficient procedure can easily be extended to the synthesis of other *gem*-difluoromethylenated α,β-unsaturated-δ-lactone moiety. In addition, the viability of RCM of high electron-deficient olefins has been demonstrated.

The similarity in size but substantial difference in electrostatic properties between fluorine and hydrogen makes fluorination an interesting strategy in the design of biologically active compounds.[1] In previous years, the *gem*-difluoromethylene moiety (CF_2) has been proved to be a key structural unit in many fluorinated compounds of biological and pharmaceutical significance.[2] This group has been recognized as an isopolar–isosteric replacement for oxygen and used as one strategy for the modification of biologically active compounds.[3]

Unsaturated lactones are structural elements commonly found in natural products of medicinal interest. Furthermore, they are often used as intermediates in the synthesis of natural products. (−)-Massoialactone,[4,5] a typical α,β-unsaturated-δ-lactone, is the major constituent of the bark oil of *Cryptocarya massoia*, isolated for the first time by Abe[6] in 1937. It is a powerful skin irritant and produces systolic standstill in frog heart muscle. (−)-Massoialactone is the allomone of the two species of formicine ants[7] belonging to the *Componotus* genus collected in Western Australia. This lactone has also been isolated from cane molasses[8] and jasmine blossoms[9] as a flavor substance. Various methods for the synthesis of massoialactone have been reported.[10] As part of our continuing interest in the preparation of *gem*-difluoromethylenated biological active compounds, now we would like to report an expeditious synthesis of 4,4-difluoromassoialactone **4**.

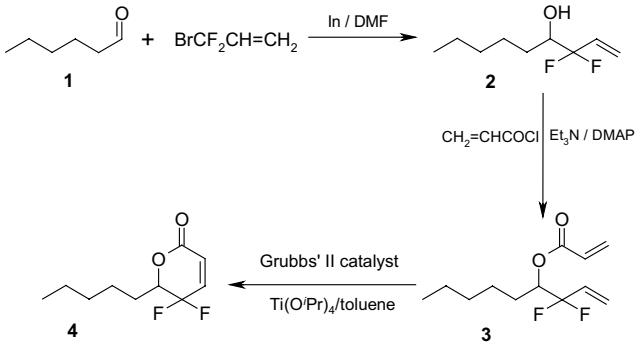


During the past few years, ring-closing metathesis (RCM) have been developed as an efficient route to achieve the synthesis of lactenones and lactones of different ring sizes.[11] Furthermore, it has been demonstrated that RCM can also be applied to olefins bearing fluorine substituents.[12,13] These results prompted us to study the use of RCM as a potentially powerful way to access *gem*-difluoromethylenated α,β-unsaturated-δ-lactone **4**.

Our synthesis of **4** commenced from aldehyde **1** (Scheme 1). The *gem*-difluoromethylene moiety was introduced by the reaction of **1** with 3-bromo-3,3-difluoropropene in the presence of indium powder[14] to yield the difluorohomoallyl alcohol **2**. Treatment of **2** with acryloyl

Keywords: Massoialactone; *gem*-Difluoromethylene-containing compounds; Ring-closing metathesis (RCM).
* Corresponding author. Tel.: +86 21 64163300; fax: +86 21 64166128; e-mail: flq@mail.sioc.ac.cn

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.188



Scheme 1.

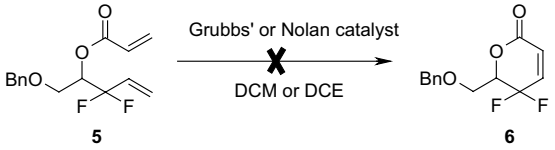
chloride and Et_3N in the presence of a catalytic amount of DMAP afforded the acryloyl ester **3**.

When our work was proceeding, Percy and co-workers[13] reported their unsuccessful attempts to get similar lactone using the same strategy (Scheme 2). Acryloyl ester **5** failed to undergo RCM to any appreciable extent in the presence of either the Grubbs' or Nolan catalysts, either in dichloromethane or 1,2-dichloroethane over 7 days. Because of the high electron-deficient properties of the substrate **3**, we anticipated that the RCM might proceed at high reaction temperature.[15]

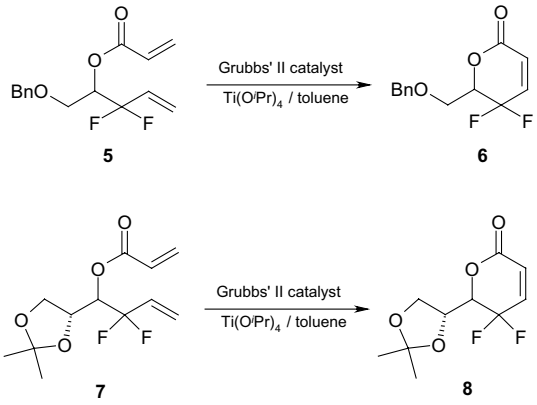
Initially, the RCM of ester **3** was carried out in toluene at reflux in the presence of 5% Grubbs'II catalyst, the reaction resulted in incomplete conversion and only a small amount of the expected product **4** was isolated. Thus, high catalyst dosage (10%) was used, which also resulted in incomplete conversion. Considering the earlier olefin metathesis catalysts often require Lewis acidic co-catalysts or promoters to improve their activities,[16] $Ti(O^iPr)_4$ was used as co-catalyst. Fortunately, acrylate ester **3** in toluene at reflux with Grubbs'II catalyst (0.08 equiv) and $Ti(O^iPr)_4$ (0.30 equiv) underwent smoothly to afford *gem*-difluoromethylenated α,β-unsaturated-δ-lactone **4** in 87% yield.[17]

To demonstrate the viability of our improved RCM reation conditions, the RCM of the same substrate **5** used by Percy and co-workers was investigated. We were pleased to find that the RCM of **5** proceeded smoothly and compound **6** was isolated in 71% yield (Scheme 3). Furthermore, treatment of compound **7** with Grubbs'II catalyst (0.08 equiv) and $Ti(O^iPr)_4$ (0.30 equiv) in toluene at reflux led to compound **8** in 69% yield (Scheme 3).

In conclusion, 4,4-difluoromassoialactone has been expeditiously prepared for the first time. The strategy



Scheme 2.



Scheme 3.

can be believed to be efficient for the synthesis of other *gem*-difluoromethylenated α,β-unsaturated-δ-lactone moiety. In addition, it may be a reference for other potential inert metathesis substrates, of which the two double bonds are both electron deficient. We are continuing our investigation in this direction.

Acknowledgements

We thank the National Natural Science Foundation of China, Ministry of Education of China, and Shanghai Municipal Scientific Committee, for funding this work.

References and notes

1. Percy, J. M. *Contemp. Org. Synth.* **1995**, 251–268.
2. For a review on *gem*-difluoromethylenated compounds, see: Tozerj, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619–8683.
3. (a) Blackburn, G. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930–932; (b) Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1119–1125; (c) Chambers, R. D.; Jaouhari, R.; O'Hagan, D. *Tetrahedron* **1989**, *45*, 5101–5108; (d) Blackburn, G. M.; Jakeman, D. L.; Ivory, J. A.; Williamson, M. P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2573–2578; (e) Burke, T. R., Jr.; Symth, M. S.; Otaka, A.; Nomizu, M.; Roller, P. P.; Wolf, G.; Care, R.; Shoelson, S. E. *Biochemistry* **1994**, *33*, 6490–6494.
4. Meijer, Th. M. *Recl. Trav. Chim. Pays-Bas* **1940**, *59*, 191–201.
5. Crombie, L. *J. Chem. Soc.* **1955**, 1007–1025, 2535.
6. Abe, S. *J. Chem. Soc. Jpn.* **1937**, *58*, 246–251.
7. Cavill, G. W. K.; Clark, D. V.; Whitfield, F. B. *Aust. J. Chem.* **1968**, *21*, 2819–2823.
8. Hashijume, T.; Kikuchi, N.; Sasaki, Y.; Sakata, I. *Agr. Biol. Chem.* **1968**, *32*, 1306–1309.
9. Kaiser, P.; Lamparsky, D. *Tetrahedron Lett.* **1976**, *17*, 1659–1660.
10. Grupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849–851, and references cited therein.
11. For recent examples, see: (a) Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929–8936; (b) Fuerstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069; (c) Buszek, K. R.; Sato, N.; Jeong, Y.

Tetrahedron Lett. **2002**, *43*, 181–184; (d) Sabitha, G.; Raddy, C. S.; Babu, R. S.; Yadav, J. S. *Synlett* **2001**, 1787–1789.
12. (a) Percy, J. M.; Pintat, S. *Chem. Commun.* **2000**, 607–608; (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784; (c) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692–1693; (d) Salim, S. S.; Bellingham, R. K.; Satchoren, V.; Brown, R. C. D. *Org. Lett.* **2003**, *5*, 3403–3406; (e) Marhold, M.; Buer, A.; Hiemstra, H.; Maarseveen, J. H.; Haufe, G. *Tetrahedron Lett.* **2004**, *45*, 57–60; (f) Matteis, V. D.; Delft, F. L.; Gelder, R.; Tiebes, J.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2004**, *45*, 959–963.
13. Audouard, C.; Fawcett, J.; Griffiths, G. A.; Percy, J. M. *Org. Biomol. Chem.* **2004**, *2*, 528–541.
14. Kirihara, M.; Takuwa, T.; Takizawa, S.; Momose, T.; Nemoto, H. *Tetrahedron* **2000**, *56*, 8275–8280.
15. Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547–550.
16. (a) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, 1997; (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.
17. Typical procedure for RCM reaction: acrylate ester **3** (71 mg, 0.31 mmol) and titanium isopropoxide (0.092 mmol) in dry toluene (19.5 mL) was refluxed for 3 h under an argon atmosphere. Then tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium(IV) dichloride (21 mg, 0.024 mmol) dissolved in toluene (4 mL) was added dropwise to the mixture over 45 min. The reaction mixture was stirred at reflux for 15 min. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether: 1/20) to give lactone **4** (54 mg, 87% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77–6.84 (m, 1H), 6.29 (d, J = 10.2 Hz, 1H), 4.41–4.54 (m, 1H), 1.27–1.90 (m, 8H), 0.89–0.93 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −109.3 (dd, J = 288.1, 17.1 Hz, 1F), −110.7 (dt, J = 287.9, 7.2 Hz, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.7, 137.9 (dd, J = 32.0, 26.7 Hz), 126.5 (t, J = 9.1 Hz), 112.7 (t, J = 241.2 Hz), 79.4 (dd, J = 31.8, 29.1 Hz), 31.3, 27.1 (d, J = 3.3 Hz), 24.3, 22.3, 13.9; IR (neat) 3075, 2961, 2935, 2864, 1750, 1644, 1469, 1267, 1124, 1068, 825 cm^{-1}; HRMS calcd for $C_{10}H_{14}O_2F_2$ (M^+) 204.0962, found 204.1000.