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Molecular complexity from aromatics: synthesis of highly functionalized spiro δ-lactones

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ABSTRACT

A novel, general, and efficient method has been developed for the synthesis of highly functionalized spiro δ-lactones from aromatic precursors. Our methodology involves a tandem oxidative dearomatization-rearrangement of tertiary furyl carbinols and ring-closing metathesis as key features. This method allows an access to the spirolactones attached to carbocycles of various sizes.

A large number of natural products, displaying diverse biological activities, possess spirolactone moiety as a key structural element in their molecular scaffold.[1] Though, spiro γ-lactones are the most common of these spirolactones,[1c,d] isolation of some complex bioactive natural products, possessing highly functionalized spiro δ-lactone has been recently reported.[2,3] Steroids bearing this motif show impressive anticancer activity.[4] Apart from others, this moiety is the key component of the molecular framework of the recently isolated alkaloid hypserpine **1**[2] and norlabdane-type diterpene, vitexifolin E **2**[3] (Fig. 1).

Spiro δ-lactones have thus emerged as an important class of compounds and have stimulated interest in the chemistry of these systems. Highly functionalized spirolactones pose considerable synthetic challenge. Installation of the functionalities for lactonization and creation of the quaternary carbon bearing these functionalities are the two main obstacles in their synthesis. Such spiro systems, though, have earlier been synthesized in some separate and isolated instances, these methods are not generally applicable.[5,6] Thus, there exists a continuous need to develop new methods for the construction of these entities.[7] In view of this and our interest in harnessing synthetic potential of aromatic compounds,[8] we embarked upon a program to develop a general, flexible, and adaptable method for the construction of highly functionalized spiro δ-lactones from commercially available furan derivatives.

Our strategy, involving oxidative dearomatization-rearrangement of furyl carbinols[9,10] and ring-closing metathesis[11] as key steps, is outlined in Scheme 1. It was considered that RCM in lactone of type **4**, containing two appended olefinic substituents at δ-position, would provide an easy access to the required spiro δ-lactone of type **3**. The disubstituted lactone **4** may be obtained by the oxidation of lactols of type **5**, which may, in turn, be derived from the oxidative rearrangement of the appropriate *tert*-furyl alcohols of type **6**.

In order to realize our objective, the furyl carbinol precursors **9**, **10**, and **11** were prepared by the nucleophilic addition of an excess of Grignard reagent, prepared from the respective ω-bromoalkene, to methyl furoate **8** (Scheme 2). The addition of 2 equiv of the nucleophile resulted in the formation of the required *tert*-alcohols in good yields.

In addition, carbinols having dissimilar olefinic tethers were also prepared as shown in Scheme 3. Thus, *tert*-alcohols **14**, **15**, and **16** were synthesized from furyl ketones **12** and **13** by the addition of appropriate Grignard reagents.

Having prepared the aromatic precursors, our next task was to subject them to oxidative dearomatization. Initially, we had some

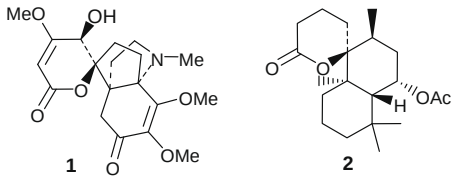

Figure 1.

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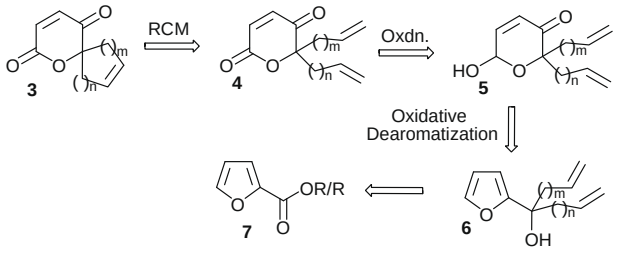
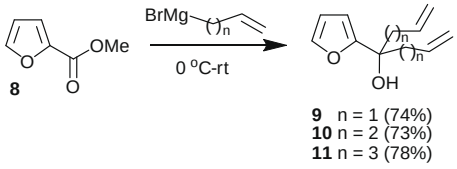


Scheme 1.

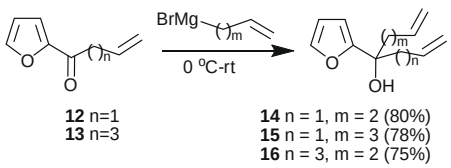


Scheme 2.

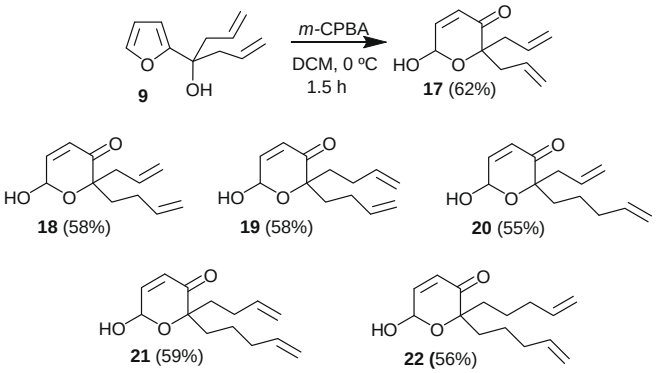
apprehension about the oxidative rearrangement of the *tert*-carbinols of type **6** as they contain several olefinic functionalities, which are quite reactive toward *per*-acid oxidants and may undergo epoxidation. Gratifyingly, after some experimentation, it was found that these carbinols indeed undergo smooth oxidative rearrangement to give the corresponding keto-lactols bearing bis-olefinic moiety. Thus, the carbinol **9** bearing two allyl groups upon treatment with *m*-chloroperbenzoic acid at 0 °C gave the corresponding lactol **17** in good yield (Scheme 4). The carbinols **10** and **11** were rearranged under similar conditions to give the lactols **19** and **22**, respectively. Similarly, rearrangement of carbinols **14**, **15**, and **16** furnished lactols **18**, **20**, and **21** (Scheme 4) as mixture of diastereomers due to generation of anomeric center during oxidative rearrangement. The diastereomeric mixture, though, was of no consequence as in the next step the anomeric hydroxyl group would be oxidized.

Thus, the disubstituted lactols were subjected to the oxidation with PCC. The lactol **17** was oxidized with PCC which gave the lactone **23** in excellent yield (Scheme 5). Similarly, the lactols **18**–**22** were also oxidized to give the lactones **24**–**28**, respectively.

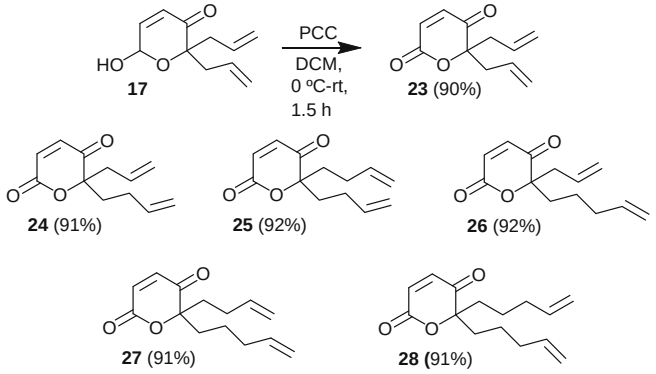
With the required lactones in hand, we focused our attention on the subsequent transformation of δ-disubstituted lactones into spiro δ- lactones *via* intramolecular ring-closing metathesis. Thus, the lactone **23** was treated with Grubbs' 1st generation catalyst[12a] (**29**) (5 mol %), at ambient temperature for 5 h, which gave the desired spirolactone **31** in 60% yield (Scheme 6). With an objective to improve the yield of the reaction, we used Grubbs' 2nd generation catalyst[12b] (**30**) (2.25 mol %), at ambient temperature. The reaction was complete in less than 2 h furnishing **31** in 75% yield. This reaction not only proved to be high yielding and faster but also required significantly lesser catalyst loading. Therefore, for all subsequent RCM reactions, we decided to use Grubbs' 2nd generation catalyst (**30**). Thus, the treatment of lactones **24**, **25**, and **26** with **30** in a similar fashion, provided the corresponding spiro compounds **32**, **33**, and **34**, respectively, in very good yields (Scheme 6).



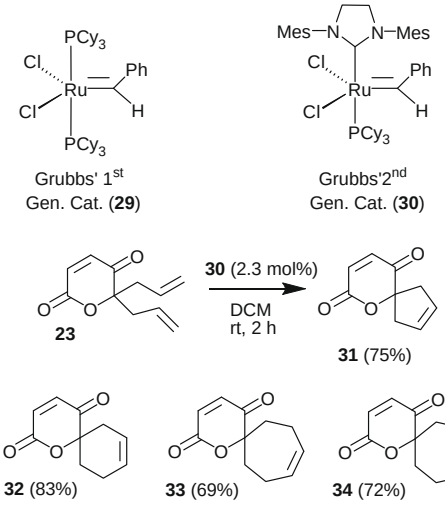
Scheme 3.



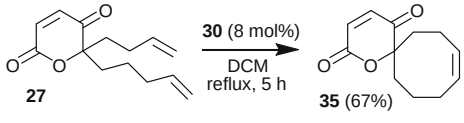
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

Owing to the entropic and steric factors, construction of medium-sized carbocycles is considered to be a challenging task.[13] In view of this it was interesting to examine the RCM of lactones **27** and **28**, which would provide eight- and nine-membered rings, respectively. Our initial attempt to bring about RCM in lactone **27** with **30** (3 mol %) was not encouraging as the reaction showed no progress at room temperature, so the reaction mixture was refluxed for 3 h followed by chromatographic purification, which provided low yield (29%) of the spirolactone **35**.[14] However, upon considerable optimization, significantly improved yield (67%) of the desired product **35** was obtained (Scheme 7).

After this encouraging result, RCM reaction of **28** was attempted. Thus, a solution of **30** in dichloromethane was added to a refluxing solution of **28** in dichloromethane. Upon completion of the reaction, and chromatographic purification of the product, it was found that the isolated material was a mixture of oligomers, resulting from the intermolecular metathesis of the starting material. All our subsequent attempts, under varying solvents, conditions, and catalysts proved to be unsuccessful.

In conclusion, we have demonstrated that simple furyl carbinols can be utilized, in an efficient manner, to gain a rapid access to the spiro δ-lactones, related to the natural product hypserpine. These densely functionalized lactones offer ample opportunities for manipulation of the spiro system in a selective manner. This method is flexible enough to permit the attachment of rings of varying sizes onto the lactone, by way of changing the length of the olefinic tether. Efforts are underway to apply this method for the synthesis of even complex spirolactones.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.019.

References and notes

1. (a) Page, C. B.; Pinder, A. R. *J. Chem. Soc.* **1964**, 4811; (b) Broadbent, J. L.; Schnieden, H. *Br. J. Pharmacol.* **1958**, *13*, 213; (c) Trost, B. M.; Balkovec, J. M.; Mao, M. K. T. *J. Am. Chem. Soc.* **1983**, *105*, 6755; (d) Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 3806; (e) Grob, J.; Boillaz, M.; Schmidlin, J.; Wehrli, H.; Wieland, P.; Fuhrer, H.; Rihs, G.; Joss, U.; De Gasparo, M.; Haenni, H.; Ramjoue, H. P.; Whitebread, S. E.; Kalvoda, J. *Helv. Chim. Acta* **1997**, *80*, 566.
2. Montagnac, A.; Gallard, J.-F.; Litaudon, M.; Sevenet, T.; Pais, M. *Nig. J. Nat. Prod. Med.* **1999**, *3*, 83.
3. Ono, M.; Yanaka, T.; Yamamoto, M.; Ito, Y.; Nohara, T. *J. Nat. Prod.* **2002**, *65*, 537.
4. (a) Bydal, P.; Auger, S.; Poirier, D. *Steroids* **2004**, *69*, 325; (b) Qiu, W.; Zhou, M.; Mazumdar, M.; Azzi, A.; Ghanmi, D.; Luu-The, V.; Labrie, F.; Lin, S.-X. *J. Biol. Chem.* **2007**, *282*, 8368; (c) Bydal, P.; Luu-The, V.; Labrie, F.; Poirier, D. *Eur. J. Med. Chem.* **2009**, *43*, 632.
5. For the synthesis of spiro δ-lactones by double alkylation method see: (a) Canonne, P.; Belanger, D.; Lemay, G.; Foscolos, G. B. *J. Org. Chem.* **1981**, *46*, 3091; (b) Canonne, P.; Belanger, D. *J. Chem. Soc., Chem. Commun.* **1980**, 125; For the synthesis of spiro α-lactones by double alkylation method see: (c) Posner, G. H.; Hamill, T. G. *J. Org. Chem.* **1988**, *53*, 6031.
6. (a) Sell, M. S.; Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1993**, *34*, 6007; (b) Rieke, R. D.; Sell, M. S.; Xiong, H. *J. Org. Chem.* **1995**, *60*, 5143; (c) Zhang, W. *Tetrahedron Lett.* **2000**, *41*, 2523.
7. For excellent reviews on various strategies used for the construction of spirocyclic compounds see: (a) Krapcho, A. P. *Synthesis* **1974**, 383; (b) Krapcho, A. P. *Synthesis* **1978**, 77; (c) Martin, S. F. *Tetrahedron* **1980**, *36*, 419; (d) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007; (e) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165.
8. (a) Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324; (b) Singh, V.; Iyer, S. *J. Chem. Soc., Chem. Commun.* **2001**, 2578; (c) Singh, V.; Iyer, S.; Mobin, S. *J. Org. Chem.* **2005**, *70*, 973.
9. (a) Achamatowicz, O., Jr.; Bukowski, P.; Szechner, B.; Swiezchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973; (b) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3361.
10. (a) Lefebvre, Y. *Tetrahedron Lett.* **1972**, *13*, 133; (b) Laliberte, R.; Medawar, G.; Lefebvre, Y. *J. Med. Chem.* **1973**, *16*, 1084.
11. (a)*Alkene Metathesis in Organic Synthesis*; Furstner, A., Ed.; Springer, 1998; (b)*Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; (c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875; (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (e) Kotha, S.; Lahiri, K. *Synlett* **2007**, 2767.
12. (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100; (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
13. Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881.
14. The experimental details and spectral data are given in the Supplementary data associated with this Letter.