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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3517–3520

Domino Wittig Diels–Alder reaction: an expeditious entry into the AB ring system of furanosesquiterpenes

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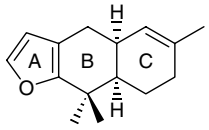
Received 7 December 2006; revised 11 March 2007; accepted 21 March 2007
Available online 24 March 2007

Abstract—A domino Wittig Diels–Alder reaction has been employed in delineating a short and flexible synthetic stratagem for ready access to the AB ring system and the tricyclic framework of furanosesquiterpenes, such as the bioactive natural products, furodysin and furodysinin.

Furanosesquiterpenes form an important and ever-expanding class of natural products.[1] Reports on their isolation from various marine invertebrates continue to appear in the literature.[2] Among the various furanosesquiterpenoids reported to date, the tricyclic natural products furodysin **1** and furodysinin **2**, first isolated in 1978 from a species of the sponge of genus *Dysidea*, are noteworthy, particularly from the viewpoint of their biological activity.[3] Apart from the ichthyotoxicity of **1** and **2**,[4] the thioacetate of the latter (**3**, SKF 105900) is a novel and specific high affinity agonist that can bind to LTB4 receptors and activate the receptor mediated signal transduction process in human PMN and U-937 cells.[5] While the total syntheses of (±)-**1** and (±)-**2** were accomplished by Hirota et al. from a *cis*-decalin derivative,[6] (+)-9-bromocamphor and *trans*-limonene oxide were employed as chirons for the enantiospecific syntheses of (−)-**1** and (−)-**2**, respectively.[7,8]



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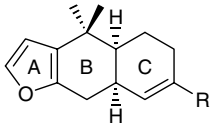

R = Me **(2)**, R = CH_2SAc **(3)**

Against this background and in keeping with our ongoing programme aimed at creating synthetic analogues of bioactive marine natural products, we decided to develop a general method for the synthesis of furanosesquiterpenes, such as **1** and **2**, bearing different substituents in the BC ring. Towards this end, it was reasoned that an appropriately functionalized B ring, appended to a furan moiety, could serve as a handle to construct the C ring in the tricyclic framework of furanosesquiterpenes. In this regard, the possibility of employing an intramolecular Diels–Alder (IMDA) cyclization[9] in tandem with a Wittig olefination on a suitably functionalized furan moiety caught our attention. Our continuing interest in domino reactions[10,11] prompted us to explore the scope of a tandem Wittig Diels–Alder reaction to build the AB ring system of furanosesquiterpenes **1** and **2**.

Our initial endeavours to this end, commenced from furfural **4**, which when subjected to a domino Wittig Diels–Alder reaction with phosphorane **5a** in refluxing diphenyl ether, afforded a diastereomeric mixture of the tricyclic γ-lactones **7a** and **8a** in 60% yield. Under identical reaction conditions, 3-furaldehyde **9**, when treated with **5a**, furnished a mixture of γ-lactones **10a** and **11a**, regioisomeric with **7a** and **8a**, respectively. Reaction of the phosphorane **5b** and either of isomeric furaldehydes, **4** and **9**, also proceeded smoothly, each yielding a mixture of the four expected diastereomeric products (as judged from ^{1}H NMR) in 60% yield, along with a minor quantity of furylacrylic acid (Scheme 1, Table 1). However, attempts to obtain a

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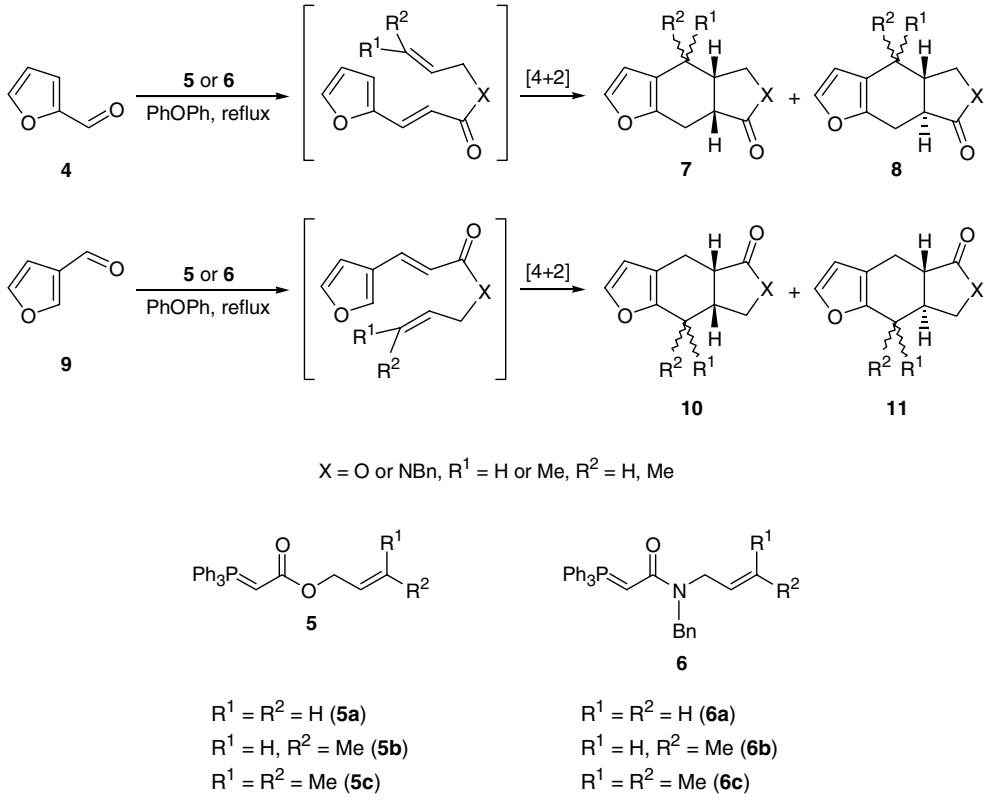
doi:10.1016/j.tetlet.2007.03.114



Scheme 1. Domino Wittig Diels–Alder reactions employed in the present study.

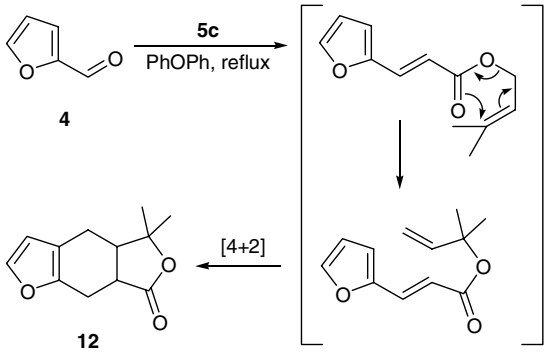
Table 1. Summary of the results of the tandem Wittig Diels–Alder reactions conducted in the present study

Aldehyde	Phosphorane	R^1	R^2	X	Products obtained	Ratio	Yield (%)
4	**5a**	H	H	O	**7a** (*syn*) + **8a** (*anti*)	1:1	60
4	**5b**	H	Me	O	**7b** (*syn*, 2 diastereomers) + **8b** (*anti*, 2 diastereomers)	3:2.3:1.8:1[a]	60
4	**5c**	Me	Me	O	Expected: **7c** (*syn*) + **8c** (*anti*); obtained: 2-furylacrylic acid + **12** (trace)		n.r.[b]
9	**5a**	H	H	O	**10a** (*syn*) + **11a** (*anti*)	1:1	60
9	**5b**	H	Me	O	**10b** (*syn*, 2 diastereomers) + **11b** (*anti*, 2 diastereomers)	3.2:3:2.4:1[a]	60
4	**6a**	H	H	NBn	**7d** (*syn*) + **8d** (*anti*)	1:1	80
4	**6b**	H	Me	NBn	**7e** (*syn*, 2 diastereomers) + **8e** (*anti*, 2 diastereomers)	9.4:7.8:1.1:1[c]	80
4	**6c**	Me	Me	NBn	**7f** (*syn*) + **8f** (*anti*)	1:1	80
9	**6a**	H	H	NBn	**10c** (*syn*) + **11c** (*anti*)	1:1	80
9	**6b**	H	Me	NBn	**10d** (*syn*, 2 diastereomers) + **11d** (*anti*, 2 diastereomers)	18.9:15.6:2.3:1[c]	80
9	**6c**	Me	Me	NBn	**10e** (*syn*) + **11e** (*anti*)	1:1	80

[a] Ratio based on ^{1}H NMR.
[b] Not recorded.
[c] Ratio based on GC–MS.

gem-dimethylated B-ring, as present in **1** and **2**, in the form of tricyclic lactones **7c** and **8c** via reaction between **5c** and **4** was prevented by the formation of a large amount of 2-furylacrylic acid along with a trace amount of **12**, a product possibly formed by an allylic ester rearrangement in the Wittig product intermediate (Scheme 2, Table 1).

At this point,[12] it was felt that replacing the ester linkage in the phosphorane with a less base labile amide functionality would not only avoid the problem of hydrolysis in the intermediate ester (Wittig product), but also serve as a method for introduction of chirality through the choice of an appropriate chiral amine. Thus, phospho-



Scheme 2. Postulated mechanism for the formation of **12**.

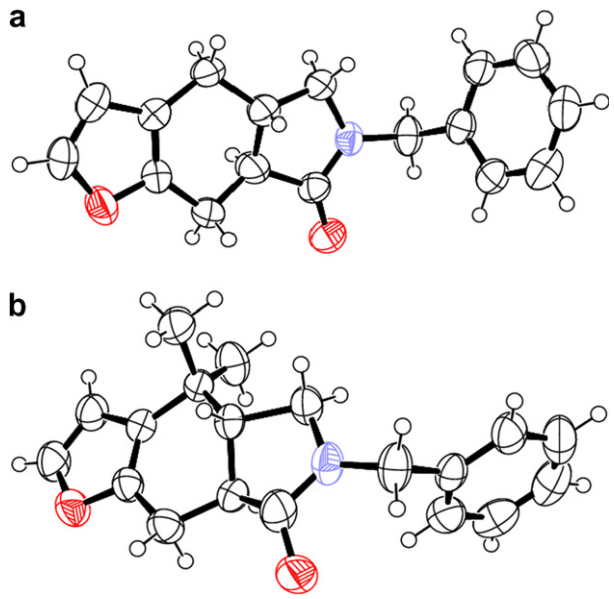


Figure 1. ORTEP figures of the *N*-benzyl substituted γ-lactams, (a) **8d**, and (b) **8f**. Displacement ellipsoids have been drawn at 50% probability level and H atoms are shown as small spheres of arbitary radii.

rane **6a** (X = NCH_2Ph) was prepared by conventional methods and when treated with **4** in refluxing diphenyl ether, gave the expected mixture of two diastereomeric *N*-benzyl substituted γ-lactams **7d** and **8d** in 80% yield. Likewise, reaction of **6a** with **9** gave the corresponding γ-lactams **10c** and **11c**, being regioisomeric with **7d** and **8d**, respectively. As observed in the case of **5b**, phosphorane **6b** reacted smoothly with both **4** and **9** to furnish a mixture of four diastereomeric lactams in each case. Much to our gratification, the domino Wittig Diels–Alder reaction of phosphorane **6c** with both **4** and **9** proceeded as predicted to give the expected mixture of two diastereomeric γ-lactams in 80% yield (Scheme 1, Table 1).

Since it was not possible to determine unambiguously the nature of the ring junction (*syn* or *anti*) in end-products **7**, **8**, **10** and **11** on the basis of NMR studies alone, recourse was taken to single crystal X-ray diffraction analysis in the case of lactam **8d** and particularly for **8f**, which both afforded crystals suitable for the diffraction studies (Fig. 1).[13]

In conclusion, we have successfully developed a short and efficient synthetic protocol, employing a domino Wittig Diels–Alder reaction, for the synthesis of the AB ring system of furanosesquiterpenes. The γ-lactam moiety in the syn-fused cycloaddition products **7f** and **10e** will be elaborated to the C-ring of **1** and **2**. The method described above will also be utilized for the development of synthetic protocols for accessing furan and other heterocyclic analogues of deoxypodophyllotoxin, naphthalene lignans and naphthofurans.[14]

Acknowledgements

We thank the University Grants Commission (UGC) and the Department of Science and Technology (DST), New Delhi for financial support. One of us, S.S., thanks the DST, India for the CCD facility at IISc, Bangalore.

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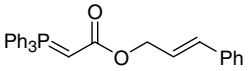
12. (a) The tandem Wittig Diels–Alder reaction between the furaldehydes **4** and **9**, and the phosphorane (shown below) was also conceptualized at this stage as a possible entry point into the synthesis of heterocyclic lignans (see Refs. 12b–d below). However, attempts to synthesize the phosphorane proved unsuccessful; (b) Hayakawa, K.; Nagatsugi, F.; Kanematsu, K. *J. Org. Chem.* **1988**, *53*, 860; (c) Ramos, A. C.; de Clairac, R. P.-L.; Medarde, M. *Heterocycles* **1999**, *51*, 1443, and references cited therein; (d) Ramos, A. C.; Palaez, R.; Lopez, L. J.; Caballero, E.; Medarde, M.; Feliciano, A. S. *Tetrahedron* **2001**, *57*, 3963.



13. Crystal data for **8d**: $C_{17}H_{17}NO_2$, $M = 267.32$, monoclinic, space group $P2_1/c$, $a = 11.479(3)$ Å, $b = 6.4481(17)$ Å, $c = 18.655(5)$ Å, $\beta = 92.839(5)°$, $V = 1379.1(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.287$ g cm^{-3}, $F(000) = 568$, $\mu = 0.084$ mm^{-1}, $R = 0.0497$, $wR = 0.1094$, GOF = 1.027 for 1540 reflections with $I > 2\sigma(I)$, CCDC-629551. Crystal data for **8f**: $C_{19}H_{21}NO_2$, M= 295.37, monoclinic, space group $P2_1/c$, $a = 7.879(2)$ Å, $b = 20.578(5)$ Å, $c = 9.851(3)$ Å, $\beta = 96.606(4)°$, $V = 1586.6(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.237$ g cm^{-3}, $F(000) = 632$, $\mu = 0.080$ mm^{-1}, $R = 0.0439$, $wR = 0.1147$, GOF = 1.045 for 2511 reflections with $I > 2\sigma(I)$, CCDC-629552. All the CIF files have been submitted to the Cambridge Crystallographic Data Centre. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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