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Synthesis of 2,5-Dihydrofurans *via* Alkylidene Carbene Insertion Reactions

Louise F. Walker,[a] Stephen Connolly[b] and Martin Wills[a]*

a. Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK.

b. Astra Charnwood, Bakewell Road, Loughborough, Leicestershire, LE11 5RH, UK.

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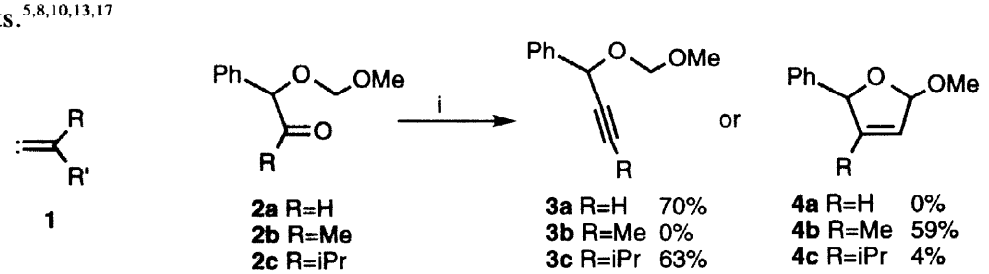
Abstract *The insertion of vinylidene carbenes into C-H bonds is an efficient method for the synthesis of 2,5-dihydrofurans. The methodology provides a convenient entry to the core structure of squalestatin/zaragozic acid natural products.*

Alkylidene carbenes **1** are valuable synthetic intermediates.[1-17] The formation of these reactive species may be conveniently achieved by a number of diverse methods,[2-17] including treatment of vinyl halides with a strong base,[2-5] nucleophilic addition to alkynyliodonium salts,[6] and by the reaction of a carbonyl compound with diazomethylphosphonate[7,8] or lithio(trimethylsilyl)diazomethane (LTDM).[9-13] Whilst it has been known for some time that carbenes **1** (R=H, R'=alkyl) undergo rapid rearrangement to alkynes,[18] analogues lacking a hydrogen atom adjacent to the carbene may participate in reactions with nearby functional groups. Intramolecular trapping of the carbene with hydroxy or amino groups provides a convenient method for the synthesis of heterocycles,[2,9,14,15] insertion of the carbenes into proximal C-H bonds provides a convenient method for the synthesis of cyclopentenes,[4,6,7,10,16,17] or heterocyclic products.[5,8,10,13,17]



Scheme 1 *Reagents and conditions;* (i) $TMSC(H)N_2$, n-BuLi, DME/hexanes

Our interest in the chemistry of vinylidene carbenes arose from studies on the total synthesis of Neohalicholactone, in which a 2,5-dihydrofuran side product was obtained *via* the insertion of a vinylidene carbene generated from a 1,1-dibromo alkene.[19] We have extended this work and report here the results of a series of systematic investigations into this valuable transformation.

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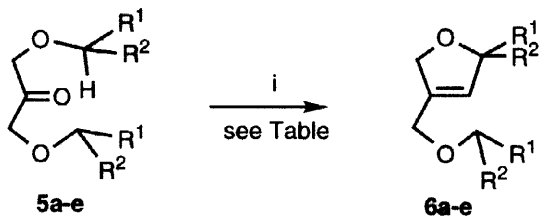
In our work we chose to use the established reagent (trimethylsilyl)diazomethane,[9-13] lithiation of which with nBuLi generates the active reagent LTDM. Our first class of substrate for study was based on the methoxymethyl-protected α–hydroxy carbonyl system **2** (Scheme 1), examples of which were conveniently prepared from mandelic acid.[20] In the case of **2a** (R=H) treatment with LTDM resulted in formation of the alkyne **3a** in excellent yield (70%), as expected.[18] No conditions could be found to modify the reaction in favour of the possible insertion process. In contrast the analogous reaction with **2b** (R=Me) resulted in clean formation of the dihydrofuran **4b** in 59% yield, apparently as a single diastereoisomer, clearly reflecting the lower migration potential of the alkyl group. The same reaction using substrate **2c** resulted in reversion to the formation of the rearrangement product **3c** as the major process. This may be the result of increased migratory ability of isopropyl due to its electron-releasing nature.[4,5]

Since it was clear that 2,5-dihydrofuran formation was favoured by electron-deficient groups on the atom adjacent to the carbene, we next examined the rearrangement of a series of symmetrical and unsymmetrical dihydroxy acetone derivatives **5a-e** (Scheme 2).[8,10,21] Throughout this series the dihydrofurans **6a-e** were the major products and only very low quantities of the alkynes were detected in the reaction mixtures. With the exception of the methoxy insertion product **6a**, isolated yields generally varied from moderate to good and were best for the benzyl-substituted substrates **5c** and **5d**. The conversion of **5e** to the hindered product **6e** proceeded in 27% yield and 48% of unchanged starting material was recovered.



Scheme 2 *Reagents and conditions;* (i) $TMSC(H)N_2$, n-BuLi, DME/hexanes

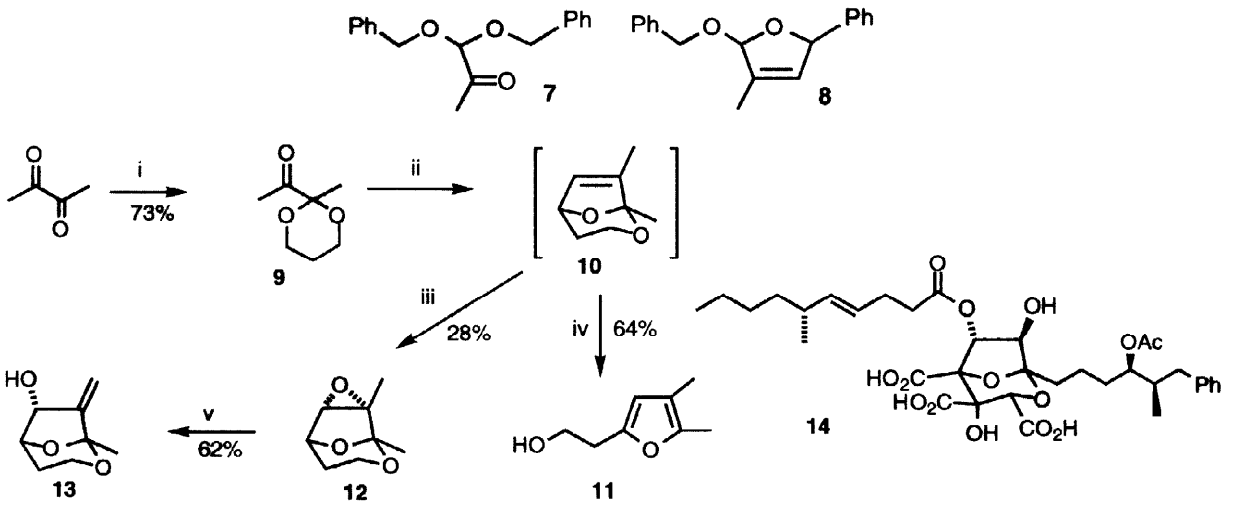
Table

Substrate	R^1	R^2	Yield **6** /%
5a	H	H	14
5b	H	Me	55
5c	H	Ph	70
5d	H	p-(MeO)C_6C_4	61
5e	Me	Me	27 +

+ 48% of unreacted starting material was recovered

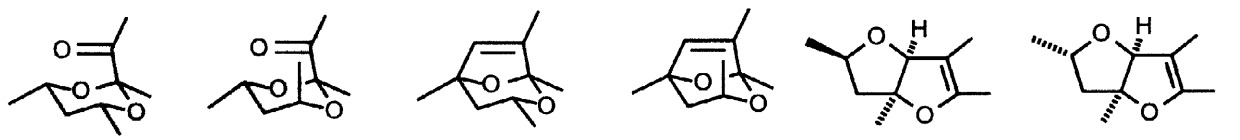
In view of the good yields of insertion reactions into benzylic C-H bonds and the low migrational aptitude of the methyl group in **2b** we next chose to examine α,α–disubstituted propanone substrate **7**.[22] Treatment with LTDM resulted in clean conversion to the dihydrofuran to give **8** as a 4:1 mixture of diastereoisomers in a 68% yield. The same reaction using the related ketal **9** (scheme 3) resulted in formation of the heterocyclic product **10** which was observed by ^{1}H-NMR of the crude product but which rearranged to the furan **11** during purification. A similar rearrangement has been noted by a group working at Glaxo-Wellcome[23] and other researchers.[8] Treatment of the crude product from **9** with dimethyldioxirane, however, resulted in formation of **12** in 28% overall yield from **9**, apparently as a single diastereoisomer. Treatment of **12** with the dianion of (1R,2S)-norephedrine resulted in ring opening to the stable allylic alcohol **13** in 62% yield. Compound **13** represents a model of the zaragozic acid/squalestatin core skeleton **14** and this approach is particularly attractive since it provides a direct access

to the structure without the problems of isomer formation which is known to occur through late-stage ketal formation used in other strategies.[24]



Scheme 3 *Reagents and conditions*: (i) $HO(CH_2)_3OH$, pTSA, toluene,hexane, (ii) $TMSC(H)N_2$, n-BuLi, DME/hexanes, (iii) Dimethyldioxirane, acetone, (iv) silica gel, (v) (1R, 2S)-norephedrine, n-BuLi, THF, PhH.

The ketalisation reactions of *meso* and *RR/SS*- 2,4-dihydroxypropanes with 2,3-butadione furnished **15a** and **15b** in yields of 55 and 70% respectively. Notably in the case of **15a** the isomer bearing an axial ketone was the major isomer of a 3:1 thermodynamic mixture and the yield above is the isolated yield of this isomer. The reactions of **15a** and **15b** with LTDM resulted, after treatment with mild acid upon workup, in the formation of the insertion/rearrangement products **17a** (45% from **15a**) and **17b** (58% from **15b**) respectively. The presumed intermediates **16a** and **16b** were observed by NMR in the crude mixture but were not isolated in these cases. The above results provide encouraging precedent for the synthesis of **14**, whilst the improved yields of rearrangement products in the cases of **17a** and **17b** confirm our expectation that the low yield of **12** is in part a result of its volatility and losses upon isolation.



In summary we have demonstrated that the insertion reactions of vinylidene carbenes with proximal C-H bonds represent a valuable method for the formation of heterocyclic systems. We are presently examining the optimisation and applications of these reactions towards the synthesis of zaragozic acids/squalestatins and our results will be presented in due course.

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References

1) P. J. Stang, *Chem. Rev.*, **1978**, *78*, 383-403

2) M. Topolski, *J. Org. Chem.*, **1995**, *60*, 5588.

3) S. Ohira, K. Yamasaki, H. Nozaki, M. Yamato and M. Nakayama, *Tetrahedron Lett.*, **1995**, *36*, 8843.

4) J. Wolinsky, G. W. Clark and P. C. Thorstenson, *J. Org. Chem.*, **1976**, *41*, 745.

5) M. S. Baird, A. G. W. Baxter, A. Hoorfar and I. Jefferies, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2575.

6) K. Schildknegt, A. C. Bohnstedt, K. S. Feldman and A. Sambandam, *J. Am. Chem. Soc.*, **1995**, *117*, 7544; T. Kosaka, T. Bando and K. Shishido, *J. Chem. Soc., Chem. Commun.*, **1997**, 1167; B. L. Williamson, R. R. Tykwinski and P. J. Stang, *J. Am. Chem. Soc.*, **1994**, *116*, 93; M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, M. Shiro and E. Fujita, *J. Am. Chem. Soc.*, **1986**, *108*, 8281; M. Ochiai, K. Uemura and Y. Masaki, *J. Am. Chem. Soc.*, **1993**, *115*, 2528.

7) J. C. Gilbert, D. H. Giamalva and M. E. Baze, *J. Org. Chem.*, **1985**, *50*, 2557; J. C. Gilbert, D. H. Giamalva and U. Weerasooriya, *J. Org. Chem.*, **1983**, *48*, 5251.

8) S. Ohira, I. Noda, T. Miobata and M. Yamato, *Tetrahedron Lett.*, **1995**, *36*, 3375; S. R. Buxton, K. H. Holm and L. Skattebol, *Tetrahedron Lett.*, **1987**, 2167

9) K. Miwa, T. Aoyama and T. Shioiri, *Synlett*, **1994**, 461; Y. Ito, T. Aoyama and T Shioiri, *Synlett*, **1997**, 1163; T. Yagi, T. Aoyama and T. Shioiri, *Synlett*, **1997**, 1063.

10) S. Ohira, K. Oka and T. Moritani, *J. Chem. Soc., Chem. Commun.*, **1992**, 721.

11) D. F. Taber and R. P. Meagley, *Tetrahedron Lett.*, **1994**, *35*, 7909; D. F. Taber, R. P. Meagley and D. J. Doren, *J. Org. Chem.*, **1996**, *61*, 5723; D. F. Taber, T. E. Christos and C. N. Hodge, *J. Org. Chem.*, **1996**, *61*, 2081; D. F. Taber and H. Yu, *J. Org. Chem.*, **1997**, *62*, 1687; S. Ohira, T. Sawamoto and M. Yamato, *Tetrahedron Lett.*, **1995**, *36*, 1537.

12) D. F. Taber, R. Walter and R. P. Meagley, *J. Org. Chem.*, **1994**, *59*, 6014; D. F. Taber, A. Sahli, H. Yu and R. P. Meagley, *J. Org. Chem.*, **1995**, *60*, 6571.

13) H. Ogawa, T. Aoyama and T. Shioiri, *Heterocycles*, **1996**, *42*, 75.

14) F. E. McDonald and A. K. Chatterjee, *Tetrahedron Lett.*, **1997**, *38*, 7687; F. E. McDonald and T. C. Olson, *Tetrahedron Lett.*, **1997**, *38*, 7691.

15) S. Kim, J.-K. Yoon and C. M. Cho, *J. Chem. Soc., Chem. Commun.*, **1996**, 909.

16) S. Kim and C. M. Cho, *Tetrahedron Lett.*, **1994**, *35*, 8405.

17) M. Kunishima, K. Hioki, S. Tani and A. Kato, *Tetrahedron Lett.*, **1994**, *35*, 7253. D. F. Taber and T. E. Christos, *Tetrahedron Lett.*, **1997**, *38*, 4927.

18) E. J. Corey and P.L. Fuchs, *Tetrahedron Lett*, **1972**, 3769.

19) D. J. Critcher, S. Connolly and M. Wills, *J. Org. Chem.*, 1997, **62**, 6638.

20) The sequence to **2a** required protection of mandelic acid methyl ester, reduction with $LiAlH_4$ and Swern oxidation. **2b / 2c** could be prepared from **2a** *via* addition of a Grignard reagent and oxidation or via reaction of a Weinreb derivative of the protected mandelic acid and a Grignard reagent.

21) Preparation of **5a-e**; reaction of 1,3-dichloroacetone with the appropriate sodium alkoxide.

22) Preparation of **7**; treatment of pyruvic aldehyde dimethyl acetal with benzyl alcohol and p-TSA.

23) M. G. Lester, G. M. P. Giblin, G. G. A. Inglis, P. A. Procopiou, B. C. Ross and N. S. Watson, *Tetrahedron Lett.*, **1993**, *34*, 4357.

24) A. Nadin and K. C. Nicolaou, *Angew. Chem., Int Edn. Engl.*, 1996, **35**, 1622.

25) D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comput. Sci.*, **1996**, *36*, 746.