Pergamon

Tetrahedron Letters 41 (2000) 9613–9616

TETRAHEDRON LETTERS

New methods for the stereoselective synthesis of 2-hydroxy-3,4-dienoates and functionalized 2,5-dihydrofurans†

Norbert Krause,* Michael Laux and Anja Hoffmann-Röder

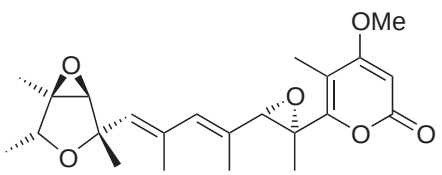
Organic Chemistry II, Dortmund University, D-44221 Dortmund, Germany

Received 1 September 2000; revised 29 September 2000; accepted 3 October 2000

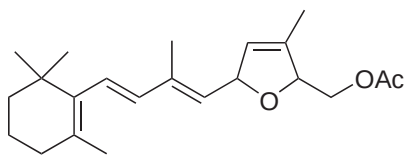
Abstract

Titanium enolates of 3,4-dienoates **3** were formed by treatment with LDA and Cp_2TiCl_2 and oxidized with dimethyl dioxirane to furnish the allenic hydroxyesters **4** with up to 90% diastereoselectivity. Smooth cyclization to the functionalized 2,5-dihydrofurans **5** was accomplished with complete axis to center chirality transfer by treatment with HCl gas in chloroform. © 2000 Elsevier Science Ltd. All rights reserved.

2,5-Dihydrofurans and derivatives thereof are pivotal structural elements of many natural products with intriguing biological activities. For instance, they are part of polyether antibiotics,[1] spiroketals[2] and mycotoxins such as verrucosidine (**1**)[3] and the structurally related citreoviridine,[4] as well as the vitamin A metabolite **2**.[5]



1



2

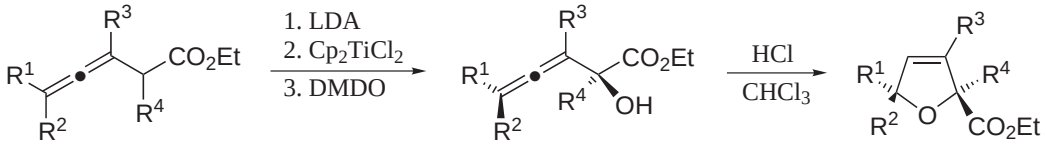
Therefore, the efficient stereoselective synthesis of these heterocyclic molecules, which is usually carried out by electrophilically induced cyclization of α-hydroxyallenes,[6,7] is highly attractive. Among different electrophiles used for this purpose, catalysis by silver salts has found particularly widespread application.[7] We now present a new stereoselective synthesis of function-

* Corresponding author.

† Dedicated to Professor Dr. Harry H. Wasserman on the occasion of his 80th birthday.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01718-4

alized 2,5-dihydrofurans **5** by oxidation of 3,4-dienoates **3** to the corresponding allenic hydroxyesters **4** and subsequent cyclization by treatment with HCl gas in chloroform.



3 **4** **5**

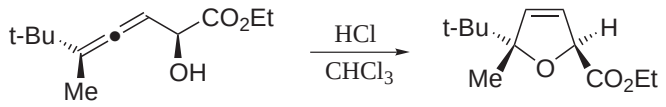
The 1,6-cuprate addition to acceptor-substituted enyes has proven to be the most efficient method for the preparation of β-allenic carbonyl compounds, giving rise to the formation of functionalized allenes of type **3** in high yield.[8] Application of Adam's protocol for the oxidation of titanium enolates with dimethyl dioxirane (DMDO)[9] to the allenyl enolate derived from *rac*-**3a** by treatment with LDA and Cp_2TiCl_2 provided 2-hydroxy-3,4-dienoate **4a** with 68% yield (46% consumption of starting material) and a diastereomeric ratio of 90:10 (Table 1, entry 1); unreacted starting material *rac*-**3a** was recovered easily by column chromatography on silica gel.

Table 1
Oxidation of titanium enolates derived from 3,4-dienoates **3** to hydroxyallenes **4** and cyclization to 2,5-dihydrofurans **5**

Entry	Substrate	R^1	R^2	R^3	R^4	Oxidation		Cyclization	
						Yield	ds	Yield	ds
1	**3a**	*t*-Bu	Me	H	H	68[a]	90:10	90	90:10
2	**3b**	*t*-Bu	Me	H	Me	63[b]	80:20	92	80:20
3	**3c**	*t*-Bu	Me	Me	H	77[c]	70:30	67	70:30
4	**3d**	*t*-Bu	*n*-Bu	H	H	67[d]	60:40	80	60:40
5	**3e**	*t*-Bu	*n*-Hex	H	Me	56[e]	60:40	83	60:40
6	**3f**	*n*-Bu	*n*-Hex	H	H	87[f]	50:50	90	50:50

[a] 46%; [b] 19%; [c] 60%; [d] 55%; [e] 30%; [f] 63% consumption of starting material.

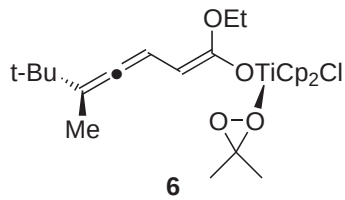
For the subsequent cyclization to the functionalized dihydrofuran **5a** we intended to take advantage of acid catalysis. Since it is known that *aqueous acid* induces isomerization of secondary and tertiary α-hydroxyallenes to the corresponding enones,[10] we treated **4a** with HCl gas in chloroform. As a matter of fact, smooth cyclization to **5a** took place which was obtained as spectroscopically pure crude product with 90% diastereoselectivity (90% yield after chromatography). Thus, similar to the previous cyclization methods,[6,7] the reaction proceeds with perfect chirality transfer, transforming the axis of chirality of **4a** into a new stereogenic center. An NOE experiment confirmed a *cis* relationship between 2-H and the methyl group at C-5 for the major diastereomer of **5a** which therefore has the (*RS*,*RS*)-configuration; consequently, the relative configuration of the major isomer of **4a** is (*RS*,*SR*).[11] The corresponding transformation of enantiomerically enriched allene (*R*)-**3a** (67% ee)[12] provided (2*S*,4*R*)-**4a** with 90% ds and 61% ee. The latter was also obtained with 87% ee by kinetic resolution of the acetate derived from *rac*-**4a** with the lipase from *Candida cylindracea*; cyclization of this enantiomerically enriched hydroxyester with HCl gas in chloroform furnished dihydrofuran (*S*,*S*)-**5a** with 90% ds and an enantiomeric excess of 85% ee.



(*2S,4R*)-**4a**
87% ee

(*S,S*)-**5a**
85% ee

In order to examine the dependence of reactivity and selectivity of the enolate oxidation on the substitution pattern of the allene, we treated the titanium enolate of 2-methyl-substituted 3,4-dienoate **3b** with dimethyl dioxirane. Due to the increased steric hindrance, the reaction proceeded sluggishly and could not be pushed beyond 19% consumption of **3b** even by warming up; nevertheless, the desired hydroxyallene **4b** was isolated with 63% yield (with regard to consumed starting material) and 80% diastereoselectivity (Table 1, entry 2).[13] Again, facile cyclization with $HCl/CHCl_3$ gave dihydrofurane **5b** with the same diastereomeric ratio (92% yield).[14] Likewise, the oxidation–cyclization sequence is not impeded by a methyl group at C-3 since analogous treatment of allene **3c** gave rise to the formation of **4c** with 70% ds (77% yield) and of **5c** with 70% ds (67% yield; entry 3). In contrast to substrates **3a**/**b** which were oxidized with 90% and 80% ds, respectively, the enolate oxidation of allenic esters **3d**/**e** bearing an *n*-butyl or *n*-hexyl group at C-5 furnished hydroxyallenes **4d**/**e** only as 60:40 mixtures of diastereomers (entries 4/5). Likewise, allene **3f** was oxidized to **4f** which was obtained as 1:1 diastereomeric mixture (entry 6). In all these cases, treatment with $HCl/CHCl_3$ served to prepare the corresponding 2,5-dihydrofurans **5d**–**f** with 80–90% yield.



6

The deprotonation of 3,4-dienoates with LDA is known to produce the *E*(*OLi*)-enolate selectively.[12] Therefore, it seems reasonable to assume that the corresponding (*E*)-titanium enolate is formed upon transmetallation which is probably coordinated by dimethyl dioxirane under the oxidation conditions. In the case of allenes with groups of different size at C-5 (**3a**–**e**), this coordination is expected to occur preferably on the diastereotopic side opposite to the bulky *t*-butyl group (intermediate **6**), and subsequent oxygen transfer on this side should produce the (*RS,SR*)-hydroxyallene. As a matter of fact, this diastereoselectivity is observed experimentally for **3a**–**e**; interestingly, allenes **3d**/**e** which bear longer alkyl chains at C-5 are oxidized with lower selectivity than the methyl-substituted substrates **3a**/**b**. In contrast, no diastereoselectivity is expected for the enolate oxidation of allene **3f** since the alkyl groups at C-5 are virtually of the same size.

Due to its simplicity and mildness, our protocol offers the opportunity to synthesize dihydrofurans with an additional ester moiety and one or two quaternary centers; thus, compared to traditional methods,[6,7] higher levels of complexity are reached which enable the assembly of more complex target molecules. Further work in this area is devoted to the improvement of reactivity and stereoselectivity of the enolate oxidation, as well as to the application of the cyclization method to amino- and mercaptoallenes.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

References

1. (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362. (b) Koert, U.; Stein, M.; Wagner, H. *Chem. Eur. J.* **1997**, *3*, 1170–1180.
2. Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661.
3. Ganguli, M.; Burka, L. T.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3762–3766.
4. Franck, B.; Gehrken, H.-P. *Angew. Chem.* **1980**, *92*, 484–486; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 461–462.
5. Yamauchi, R.; Miyake, N.; Kato, K.; Ueno, Y. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1529–1532.
6. (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984; pp. 138–141. (b) Gelin, R.; Gelin, S.; Albrand, M. *Bull. Soc. Chim. Fr.* **1972**, 1946–1949. (c) Beaulieu, P. L.; Morisset, V. M.; Garratt, D. G. *Tetrahedron Lett.* **1980**, *21*, 129–132. (d) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1990**, *55*, 2995–2996. (e) Corey, E. J.; Jones, G. B. *Tetrahedron Lett.* **1991**, *32*, 5713–5716. (f) Aurrecoechea, J. M.; Solay, M. *Tetrahedron Lett.* **1995**, *36*, 2501–2504.
7. (a) Olsson, L.-I.; Claesson, A. *Synthesis* **1979**, 743–745. (b) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 4913–4918.
8. (a) Krause, N.; Gerold, A. *Angew. Chem.* **1997**, *109*, 194–213; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186–204. (b) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1–11. (c) Krause, N.; Zelder, C. In *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed.; Wiley: New York, 2000; Vol. 2, pp. 645–691.
9. (a) Adam, W.; Hadjiarapoglou, L. *Top. Curr. Chem.* **1993**, *164*, 45–62. (b) Adam, W.; Müller, M.; Prechtl, F. *J. Org. Chem.* **1994**, *59*, 2358–2364.
10. Gelin, R.; Gelin, S.; Albrand, M. *Bull. Soc. Chim. Fr.* **1972**, 720–723.
11. The (*RS*,*RS*)-diastereomer of **4a** was obtained with 97% diastereoselectivity from ethyl 6,6-dimethyl-2-hepten-4-ynoate by epoxidation with dimethyl dioxirane and *anti*-selective copper-catalyzed S_N2'-substitution with MeMgBr. Cyclization with HCl gas in chloroform gave (*RS*,*SR*)-**5a** with 97% ds and 90% yield. Details will be published elsewhere.
12. Laux, M.; Krause, N.; Koop, U. *Synlett* **1996**, 87–88.
13. **4b**: ^{1}H NMR (C_6D_6, *=major diastereomer): $\delta = 0.90$ (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 1.01/1.02* (2s, 9H, $C(CH_3)_3$), 1.58 (s, 3H, 2-CH_3), 1.60*/1.63 (2d, $J = 2.7$ Hz, 3H, 5-CH_3), 3.51 (s, 1H, OH), 3.90*/ 3.91 (2q, $J = 7.2$ Hz, 2H, OCH_2), 5.36*/5.37 (2q, $J = 2.7$ Hz, 1H, 3-H). ^{13}C NMR (C_6D_6): $\delta = 14.0$ (+, CH_2CH_3), 14.9 (+, 5-CH_3), 24.9*/25.2 (2+, 2-CH_3), 29.1 (+, $C(CH_3)_3$), 33.7 (x, C-6), 61.6 (–, OCH_2), 97.2*/97.3 (2+, C-3), 113.2*/113.4 (2x, C-5), 175.6/175.8* (2x, C-1), 199.1 (x, C-4).
14. **5b**: ^{1}H NMR ($CDCl_3$): $\delta = 0.82$ (s, 9H, $C(CH_3)_3$), 1.14 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.19 (s, 3H, 5-CH_3), 1.40 (s, 3H, 2-CH_3), 3.96–4.13 (m, 2H, OCH_2), 5.61 (d, $J = 6.0$ Hz, 1H, 4-H), 5.75 (d, $J = 6.0$ Hz, 1H, 3-H). ^{13}C NMR ($CDCl_3$, *=major diastereomer): $\delta = 14.0$*/14.1 (2+, CH_2CH_3), 21.9 (+, 5-CH_3), 23.5/24.0* (2+, 2-CH_3), 26.1 (+, $C(CH_3)_3$), 36.7*/37.2 (2x, $C(CH_3)_3$), 60.8/61.0* (2–, OCH_2), 89.2*/89.8 (2x, C-2), 96.1/96.7* (2x, C-5), 128.4*/128.7 (2+, C-3), 133.4/134.2* (2+, C-4), 174.1 (x, CO_2CH_2).