Pergamon

Tetrahedron Letters 41 (2000) 9977–9980

TETRAHEDRON LETTERS

Toward the synthesis of the antibiotic tetrodecamycin†

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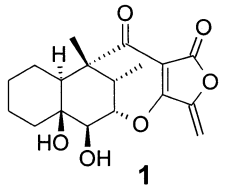
Received 12 September 2000; accepted 11 October 2000

Abstract

We report here a short approach to a tricyclic substructure of tetrodecamycin exhibiting a unique ring skeleton utilising an acid catalysed ring closure as the key step. In addition an efficient three-step synthesis of 5-alkylidene 4-methoxy-2(5*H*)-furanones starting from 4-methoxy-2(5*H*)-furanone is described.

Keywords: antibiotics; furanones; cyclisation.

Tetrodecamycin **1** is a novel tetronic acid based antibiotic isolated from the culture broth of *Streptomyces nashvillensis* MJ885-mF8. It shows distinct activity against Gram-positive bacteria including *Bacillus anthracis* as well as methicillin resistant *Staphylococcus aureus* (MRSA).[1] On the other hand dihydrotetrodecamycin **2**, isolated together with **1** from the *Streptomyces* strain, does not show such an effect revealing the crucial role of the *exo*-methylene moiety in **1** for antibacterial activity.[2] The unique ring skeleton and absolute stereochemistry of compound **1** were fully elucidated by spectral means and X-ray crystallography.[3,4] However, so far no approach to the total synthesis of **1** or **2** has been reported.



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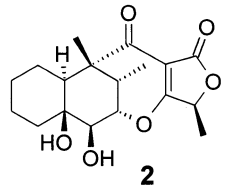

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Our retrosynthetic analysis of the skeleton of **1** is outlined in Scheme 1. The tetracyclic intermediate **3** was envisioned to arise from two key operations: (a) the hydroxyalkylation of the known 4-methoxy-5-methylene-2(5*H*)-furanone (**6a**)[5] with chiral aldehyde **5** followed by an

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† Dedicated to Professor Dr. Dr. h.c. F. Eiden on the occasion of his 75th birthday.

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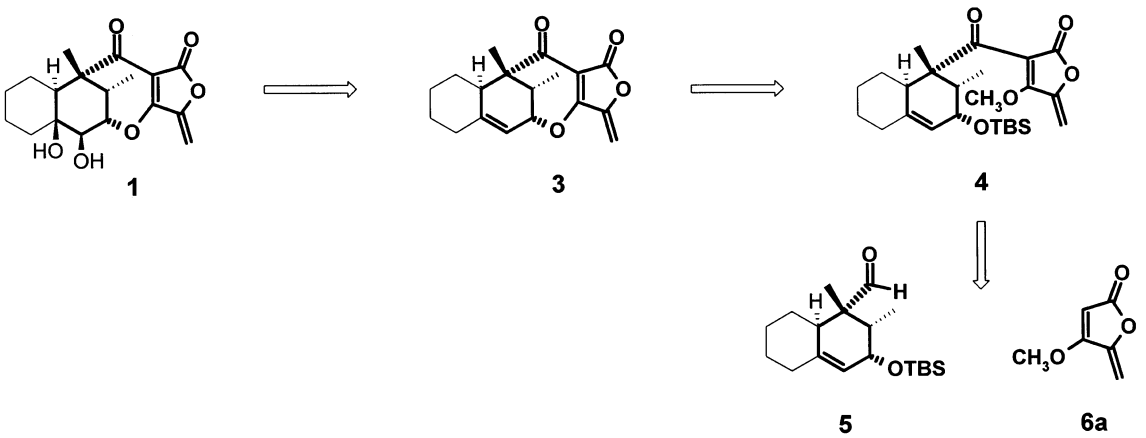
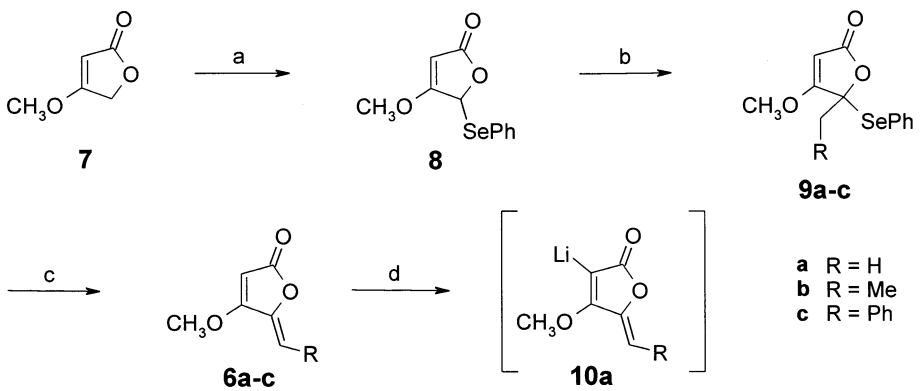
PII: S0040-4039(00)01809-8



Scheme 1.

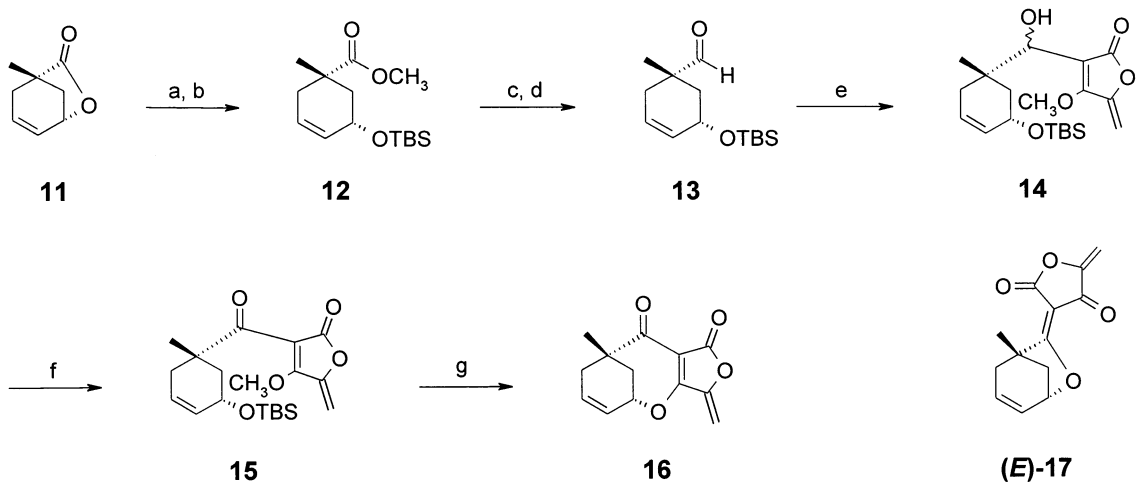
oxidation step to give **4**,[6] and (b) deprotection of the allylic hydroxyl group followed by ring closure. Having compound **3** available stereoselective *cis* dihydroxylation should provide the target molecule **1** in a single step. In this letter we describe our approach to a tricyclic substructure of **3** (bold type in Scheme 1) containing the crucial seven-membered ring.

We selected 4-methoxy-5-phenylseleno-2(5*H*)-furanone (**8**), readily prepared from commercially available 4-methoxy-2(5*H*)-furanone (**7**), as the key intermediate for a new, short and efficient approach to building block **6a** as well as to 5-alkylidene 4-methoxy-2(5*H*)-furanones in general (Scheme 2).[7] Alkylation of **8** and subsequent oxidative removal of the phenylseleno group using MCPBA gave the 5-alkylidene derivatives **6a**–**c**[8] in good overall yields (56–68% from **7**). The success of the alkylation reactions to form **9a**–**c**, however, was strongly dependent on the bases employed. Generating the enolate with *n*-BuLi resulted in the cleavage of the C5–Se bond to a considerable extent.[9] Thus in the case of the methylation reaction compound **9a** was obtained in only moderate yield (52%). This side-reaction could be avoided using *tert*-BuLi as the base, resulting in substantially higher yields of the alkylation products (**9a**: 82%).



Scheme 2. (a) (i) *n*-BuLi, THF, −78°C; (ii) PhSeCl, −78°C (90%); (b) (i) *tert*-BuLi, THF, −78°C; (ii) RCH_2X, −78°C to rt [**9a**: (R = H, X = I) 82%; **9b**: (R = Me, X = I) 65%; **9c**: (R = Ph, X = Br) 76%]; (c) MCPBA, CH_2Cl_2, 0°C [**6a**: 92%; **6b**: 95%; **6c**: 91%]; (d) LDA, THF, −78°C

The synthesis of our tricyclic target molecule **16** was initiated by opening the known bicyclic lactone **11**, readily available from 1-methyl-3-cyclohexenoic acid[10] using NaOMe to obtain the corresponding alcohol which was protected as a *tert*-butyl-dimethylsilyl ether to form **12** in 70% overall yield (Scheme 3). DIBAL reduction of the ester **12** yielded the primary alcohol which was converted to the aldehyde **13** by Swern oxidation (84% from **12**). Hydroxyalkylation of **6a** was achieved by converting **6a** first into the α-lithio derivative **10a**[6b,c] and then by reacting it with the aldehyde **13** to form **14** in 73% yield (1:1 mixture of diastereomers). Swern oxidation of the hydroxyalkylation product **14** gave acyl tetronate **15** in satisfactory yield (78%) whereas use of other oxidants (e.g. MnO_2, PDC) resulted in distinctly lower yields. Finally the key step in our synthesis—deprotection of the *tert*-butyldimethylsilyl protected hydroxyl group in **15** followed by cyclisation to give **16**—was carried out in a one pot reaction by treating **15** with 2.5 equiv. H_2SO_4 (96%) in CH_2Cl_2 at 0°C for 1 h. Thus compound **16** was isolated in good yield (70%).[11] Application of the more 'classic' silyl ether cleavage conditions, 5–10% HF (48%) in acetonitrile at 0°C, led to the formation of **16** in varying yields (up to 55%). In these cases the product was also accompanied with considerable amounts of the regioisomeric cyclisation product **17** (~1:1 mixture of *E*–*Z* isomers).[12]



Scheme 3. (a) NaOMe, MeOH, rt; (b) TBDMSCl, imidazole, DMF, rt (70% from **11**); (c) DIBAL, THF, −78°C; (d) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60°C to rt (84% from **12**); (e) **10a**, −78°C to −40°C (73%); (f) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60°C (78%); (g) H_2SO_4, CH_2Cl_2, 0°C (70%)

In conclusion, we have developed an efficient approach to a substructure of the tetrodecamycin **1** ring skeleton (seven steps, 23% overall yield). Further investigations toward the total synthesis of **1** are now in progress in our laboratory.

Acknowledgements

We are greatly indebted to Professor Dr. Klaus Th. Wanner for his generous support.

References

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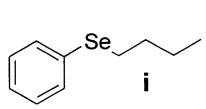
6. For prior synthesis of 3-acyl 5-alkylidene 4-methoxy-2(5*H*)-furanones following a similar strategy, see: (a) Ley, S. V.; Wadsworth, D. J. *Tetrahedron Lett*. **1989**, 1001–1004. (b) Hori, K.; Nomura, K.; Mori, S.; Yoshii, E. *J. Chem. Soc., Chem. Commun*. **1989**, 712–713. (c) Clemo, N. G.; Pattenden, G. *Tetrahedron Lett*. **1982**, 581–584.
7. Compound **6a** has been prepared from **7** by Yoshii et al. in 72% overall yield following a four-step protocol (Ref. 5). However, this strategy is not applicable to 5-alkylidene 4-methoxy-2(5*H*)-furanones in general. For a prior synthesis of 5-alkylidene 4-methoxy-2(5*H*)-furanones starting from **7**, see: Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Wynn, L.; Pardasani, P.; Hänsel, R. *J. Chem. Soc., Perkin. Trans. 1* **1987**, 717–742.
8. In the case of compounds **6b** and **6c** *Z*-isomers were formed exclusively; **6b**: Clemo, N. G.; Gedge, D. R.; Pattenden, G. *J. Chem. Soc., Perkin. Trans. 1* **1981**, 1448–1453.; **6c**: Ref. 7.
9. This reaction is likely to proceed by attack of *n*-BuLi on the selenium atom to form **i** and the lithium enolate of **7** which is alkylated subsequently to yield **ii** (R = H, CH_3, Ph) or is protonated during aqueous workup to yield **7**. By-products **i** and **ii** as well as compound **7** were found in the crude reaction mixtures and identified by comparison with authentic material.



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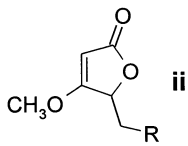

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10. Stork, G.; Logusch, E. W. *Tetrahedron Lett*. **1979**, 3361–3364.
11. All new compounds were characterised by ^{1}H and ^{13}C NMR spectra and gave satisfactory elemental analyses. Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.22$ (s, 3H, CH_3), 1.98 (m, 1H,), 2.13 (dd, $J = 6.4/16.5$ Hz, 1H), 2.47 (m, 1H), 2.71 (m, 1H), 5.23 (d, $J = 2.8$ Hz, 1H), 5.31 (d, $J = 2.8$ Hz, 1H), 5.34 (m, 1H), 5.76 (m, 1H), 6.18 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.91$, 34.42, 37.38, 44.82, 76.10, 96.10, 102.61, 121.47, 135.17, 148.17, 164.19, 164.45, 198.59.
12. A closely related structure has been proposed by Boll et al. for dehydrocarolic acid **iii**, a metabolite of *Penicillium cinerascens*:[13] Jacobsen, J. P.; Reffstrup, T.; Cox, R. E.; Holker, J. S. E.; Boll, P. M. *Tetrahedron Lett*. **1978**, 1081–1084.

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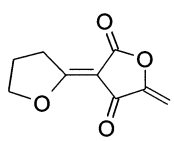

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