Tetrahedron Letters, Vol. 34, No. 44, pp. 6977-6980, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

STUDIES ON THE TOTAL SYNTHESIS OF LACTACYSTIN. AN IMPROVED ALDOL COUPLING REACTION AND A β-LACTONE INTERMEDIATE IN THIOL ESTER FORMATION

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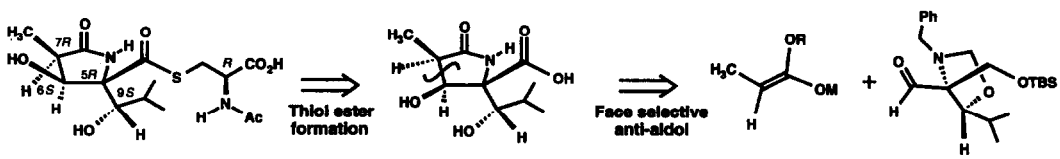
Summary: *The recently developed total synthesis of lactacystin (1) has been improved by using the zirconium enolate derived from (R)- or (S)-2-siloxy-1,2,2-triphenylpropionate which lead stereospecifically to either (6S,7R) or (6R,7S) lactacystin, respectively. The formation of the thiol ester in the synthesis of 1 proceeds mainly via a β-lactone intermediate.*

Recently we reported the first total synthesis[1] of the neurotrophic factor lactacystin.[2,3] A key step in the synthesis involved the construction of the C(6)-C(7) subunit by a *si* face selective anti-aldol coupling using the lithium enolate of 2,6-dimethylphenylpropionate[4] and aldehyde **3**. Although this reaction has since been improved from that originally reported,[5] the moderate facial selectivity (3 : 2) has limited the isolated yield of the desired (6*S*,7*R*) diastereomer to 56%. We describe herein studies on the improvement of this bond construction by the use of the zirconium enolate derived from 2-siloxy-1,2,2-triphenylpropionate[6] in a diastereofacial selective anti-aldol reaction with aldehyde **3**. Finally, we report the isolation of a highly stable bicyclic β-lactone derived from β-hydroxy acid **2**, and its bearing on the mechanism of the thiol ester formation from **2** and esters of *N*-acetylcysteine.



1 **2** **3**

The diastereoselectivity of the reaction of aldehyde **3** with the lithium enolate of 2,6-dimethylphenylpropionate under Pirrung-Heathcock conditions[4] could not be improved much by the use of other silyl ether analogs; the observed aldol facial selectivities were 1.5 : 1 for **3**, 1 : 1 for the triethylsilyl analog, and 2 : 1 for the *tert*-butyldiphenylsilyl analog. Apparently, the benzyl and isopropyl substituents on the oxazoline ring of **3** are *cis* to one another in the transition state resulting in little steric difference in nucleophilic

attack at the *re* and *si* faces of the formyl carbon (see Figure 1). The application of the chiral zirconium enolates of 2-siloxy-1,2,2-triphenylpropionate[6] in the aldol reaction with aldehyde **3** was therefore investigated.

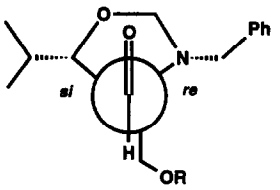
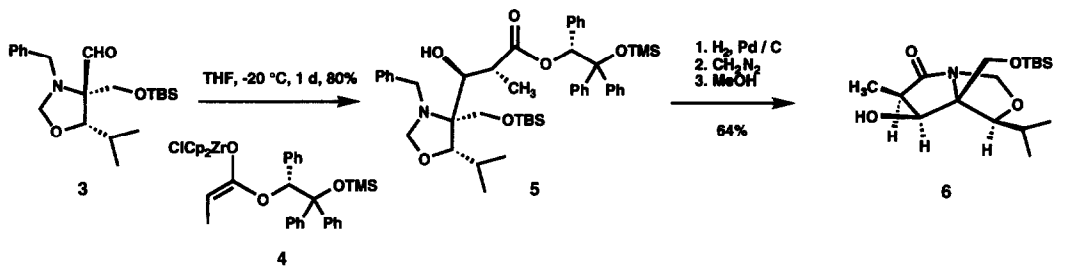
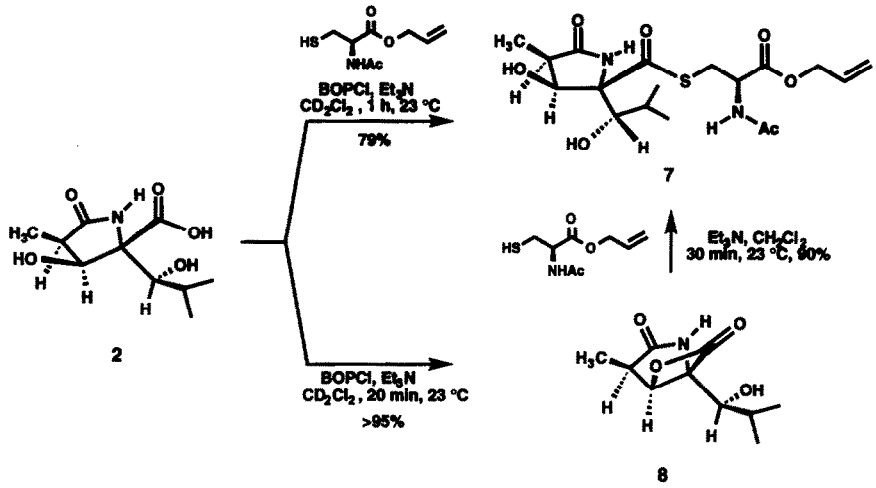


Figure 1

It was found that reaction of **3** with 2 eq of the zirconium enolate **4** at -20 °C for 12 h followed by an additional 2 eq of **4** for a further 12 h resulted in complete conversion to four diastereomeric aldol products in a ratio of 32:2:2:1 with the (6*S*,7*R*) diastereomer (**5**) being isolated in 80% yield[7,8] after silica gel chromatography. Although simple unfunctionalized aldehydes react completely with **4** at -105 °C in 3 h,[6] these conditions resulted in complete recovery of aldehyde **3**. The use of excess zirconium enolate **4**, higher temperatures, and longer reaction times were essential for an optimal yield of **5**. Hydrogenation of **5**, followed by diazomethane treatment and subsequent cyclization in methanol (4 h, 50 °C) provided **6**, identical with an authentic sample.[1] When the enantiomer of propionate **4** was employed, the (6*R*,7*S*) diastereomer derived from *re* face attack predominated.[9]



The improved synthesis of **6** allowed the synthesis of gram quantities of β-hydroxy acid **2**. As reported, **2** was coupled selectively with *N*-acetylcysteine allyl ester without hydroxyl protection using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl)–triethylamine to provide lactacystin allyl ester (**7**).[1] Due to the proximity of the unprotected *cis* hydroxyl functionality, we were curious as to the possibility that the thiol ester coupling proceeded via the β-lactone **8**.



Treatment of **2** (0.2 M) alone with BOPCl (1.2 eq) and triethylamine (3 eq) in dichloromethane-d_2 at 23 °C resulted in rapid, clean formation (>95% conversion, 76% isolated yield) of the β-lactone **8** after 20 min as a stable, colorless, crystalline solid, mp 185 °C (dec), the structure of which was determined by ^{1}H NMR, IR, mass spectral analysis and confirmed by X-ray analysis.[10,11] Reaction of **8** (0.2 M) with *N*-acetylcysteine allyl ester (1.2 eq) and triethylamine (3 eq) in dichloromethane resulted in conversion (>30 : 1) to lactacystin allyl ester **7**, after 30 min at 23 °C.

Correspondingly, the coupling of **2** (0.2 M) with *N*-acetylcysteine allyl ester (1.2 eq) and triethylamine (3 eq) in dichloromethane-d_2 was monitored by ^{1}H NMR in 5 min intervals over the course of the reaction. After 2 min, the reaction had progressed to 50% completion providing both β-lactone **8** and lactacystin allyl ester **7** in a ratio of ca 1 : 1. After 10 min (75% conversion), the ratio of **8** : **7** was 1 : 2 and after 30 min (starting material was consumed), the ratio of products **8** : **7** was 1 : 10. The opening of the remaining β-lactone **8** to **7** progressed smoothly and was complete after 60 min. This study shows that the β-lactone **8** is an important intermediate in the formation of the thiol ester **7** from **2**, thiol and BOPCl. Some thiol ester **7** may form from **2** via the corresponding BOP mixed anhydride by a route of secondary importance at the concentrations reported above.

In summary, we have shown that the aldol reaction of the chiral zirconium enolate derived from 2-siloxy-1,2,2-triphenylpropionate with the aldehyde **3** proceeds with very good diasterofacial and anti-selectivity and allows the controlled synthesis of either the (6*S*,7*R*) or (6*R*,7*S*) aldol product. The β-lactone **8** is of interest not only for its stability and ease of synthesis, but as an interesting candidate for biological study.[12]

References and Notes

1. Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677-10678.
2. Ōmura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113-116.
3. Ōmura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117-118.
4. Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727-1728.
5. The yield of this transformation has been improved from 78% to 93% overall providing 56% of the desired (6*S*,7*R*) diastereomer and 37% of the (6*R*,7*S*) diastereomer on multigram quantities after silica gel chromatography. The (6*R*,7*S*) diastereomer has been used for the preparation of analogs of lactacystin, see preceding paper.
6. Braun, M.; Sacha, H. *Angew. Chem. Int. Ed. Engl.* **1991**, *10*, 1318-1320.
7. Isolated yields of 84-85% were typical, however, despite careful chromatographic purification, a small amount (*ca* 3%) of a slightly more polar isomer was present.
8. Physical data for **5**: R_f sm: 0.50; prod: 0.32 (toluene, PMA); $[\alpha]_D^{23}$ +27.2° (*c* 0.75, benzene); FTIR (film) 2957, 2930, 2858, 1740, 1735, 1719, 1456, 1251, 1154, 1106 cm^{-1}; ^1H NMR (500 MHz, benzene) δ 7.50 (br d, *J*=7 Hz, 2H, Ph-H), 7.40 (br d, *J*=7 Hz, 2H, Ph-H), 7.28 (br d, *J*=7 Hz, 2H, Ph-H), 6.94-7.2 (m, 14H, Ph-H), 4.40 (d, *J*=2.0 Hz, 1H, OCH_2O), 4.32 (m, 2H, OCH_2O, $H_3CCHCHOH$), 4.27 (d, *J*=13.3 Hz, 1H, $PhCH_2$), 4.08 (s, 2H, CH_2OSi), 3.91 (d, *J*=13.3 Hz, 1H $PhCH_2$), 3.86 (d, *J*=5.1 Hz, 1H, $OCHCH(CH_3)_2$), 3.79 (brd, *J*=5 Hz, 1H, OH), 3.13 (dq, *J*=7, 7 Hz, 1H, $H_3CCHCHOH$), 2.07 (m, 1H, $CH(CH_3)_2$), 1.27 (d, *J*=7.1 Hz, 3H, $H_3CCHCHOH$), 1.07 (d, *J*=6.6 Hz, 3H, $CH(CH_3)_2$), 0.93 (d, *J*=6.7 Hz, 3H, $CH(CH_3)_2$), 0.89 (s, 9H, $C(CH_3)_3$), 0.11 (s, 3H, CH_3Si), -0.01 (s, 3H, CH_3Si), -0.03 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 144.3, 143.5, 139.9, 137.6, 129.6, 129.3, 129.2, 128.7, 128.5, 127.6, 127.3, 127.1, 86.1, 85.3, 83.4, 79.2, 74.2, 69.9, 62.5, 52.1, 43.4, 29.2, 25.9, 22.0, 19.3, 18.1, 16.4, 2.1, -5.8, -5.9; HRMS (FAB, M+Na^+) *m/e* calc'd for $[C_{47}H_{65}NO_6Si_2Na]^+$: 818.4247, found 818.4258.
9. This observation is consistent with the results reported by Braun et al.[6] with unfunctionalized aldehydes.
10. Physical data for **8**: mp 185 (dec); R_f sm: 0.17 (EtOAc/MeOH/HOAc 40:10:1; prod: 0.65 (EtOAc, PMA); $[\alpha]_D^{23}$ -93.9° (*c* 0.53, CH_3CN); FTIR (CH_2Cl_2) 3687, 3602, 3410, 1840, 1731, 1640 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 10.5 (s, 1H, NH), 7.85 (d, *J*=6.8 Hz, 1H, OH), 5.68 (d, *J*=6.1 Hz, 1H, $H_3CCHCHOC{=}O$), 4.33 (dd, *J*=3.6, 6.7 Hz, 1H, $OCHCH(CH_3)_2$), 3.03 (dq, *J*=6.1, 7.4 Hz, 1H, $H_3CCHCHOC{=}O$), 2.09 (m, 1H, $CH(CH_3)_2$), 1.45 (d, *J*=7.5 Hz, 3H, $H_3CCHCHOH$), 1.10 (d, *J*=6.9 Hz, 3H, $CH(CH_3)_2$), 0.98 (d, *J*=6.7 Hz, 3H, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, pyridine-d_5) δ 177.4, 172.4, 80.5, 77.0, 70.6, 38.9, 29.8, 20.4, 16.5, 8.8; HRMS (FAB, M+NH_4^+) *m/e* calc'd for $[C_{10}H_{19}N_2O_4]^+$: 231.1344, found: 231.1354.
11. We wish to thank Mr. Sepehr Sarshar for the determination of the X-ray structure of **8**. Empirical Formula $C_{10}H_{15}NO_4$ (213.2) Orthorhombic space group $P_{2_12_12_1}$, *a*= 7.318(1) Å, *b*=8.256(1) Å, *c*=18.590(1) Å, V=1123.21(13) $Å^3$, Z=4, d=1.261 mg/cm^3; Mo-K_α radiation (23 °C); reflections collected 1415, independent collections 1151, observed reflections 947 (F>4.0 σ(F)), R-index=0.0493, GOF=1.03.
12. This research was supported by grants from the National Science Foundation and the National Institutes of Health.

(Received in USA 7 July 1993; accepted 26 August 1993)