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An Asymmetric Synthesis of (R)-(+)-2-Nonyl-2-(Carbomethoxy) Cyclopentanone, a Known Precursor of the Antibiotic (-)-Malyngolide

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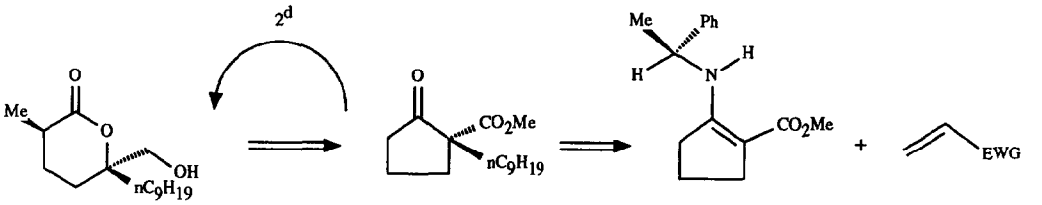
Key words : Chiral β-enamino ester, asymmetric synthesis, Lewis acid, (−)Malyngolide.

***Abstract** : A synthesis of (R)-(+)-2-nonyl-2-(carbomethoxy)cyclopentanone 2 via an asymmetric Michael process involving the chiral β-enamino ester (+)-3 is described.*

(−)Malyngolide **1**, an antibiotic isolated from a blue-green algae, exhibits significant activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*. Since its structure determination was established in 1979 [1], several asymmetric syntheses have been reported [2]. Interestingly, it has been shown in one of these syntheses [2d] that the β-keto ester(+)-**2** can be stereoselectively transformed into (−)-**1** in three steps. We have already established [3] that the reaction of chiral β-enamino esters, such as (+)-**3**, with electrophilic alkenes **4**, is an effective process for the preparation of α,α-disubstituted β-keto esters in good chemical and optical yields. The feasibility of such a process required a Lewis acid catalysis or the application of high pressure. Its application to the asymmetric synthesis of (+)-**2** based on the strategy outlined in Scheme **1**, is the subject of the present communication.

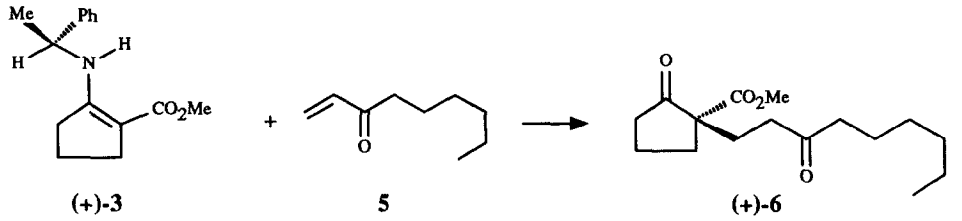


(−)-**1** (+)-**2** (+)-**3** **4**

EWG = COR, CO_2R

Scheme 1

We first examined the possibility of introducing the nine carbon atoms side chain in one single operation. Toward this end, the addition of (+)-**3** to hexyl vinyl ketone **5** was first considered. The reaction took place rapidly at -78 °C in ether (ratio **3**:**5** : $ZnCl_2$ = 1:1,5:1) to afford, after hydrolytic work-up, (+)-**6** [4,5] in 82 % yield (Scheme 1).

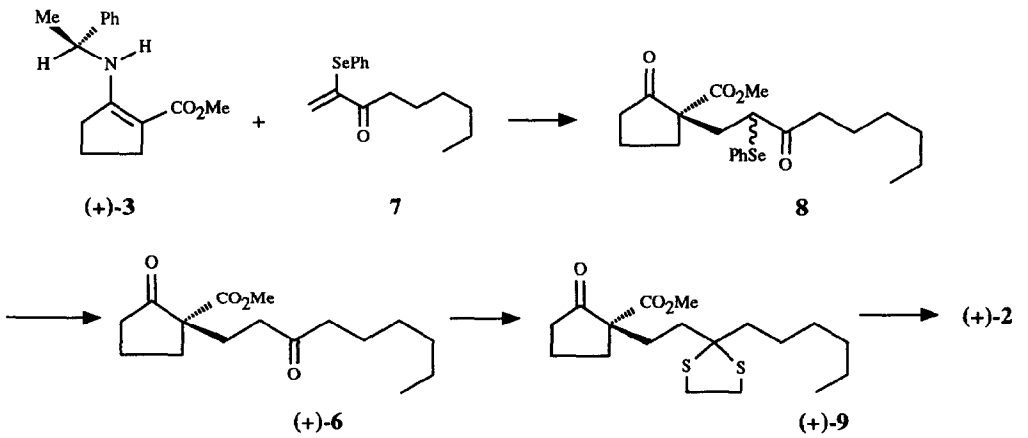


(+)-3 5 (+)-6

Scheme 2

An alternative route to (+)-**6**, making use of the activated enone **7** [6], was also successful. The reaction was carried out in THF at 0 °C for 2 days. There was thus obtained, after hydrolytic work-up (5 % aq. AcOH, THF, 20 °C, 1 h) a 55 % yield of **8** as a 4/1 mixture of isomers [7]. Treatment of this mixture with Bu_3SnH (1.5 eq., c.a AIBN, toluene at reflux) provided (+)-**6** [5] in 90 % yield (Scheme 3). Comparison of the specific rotations measured for (+)-**6** showed the asymmetric induction to be similar in both approaches. The enantiomeric excess was determined to be 70 % by ^1H NMR analysis in the presence of Eu $(hfc)_3$.

Proceeding on to reach the target β-keto ester (+)-**2** we anticipated that chemoselective protection of the less encumbered side chain carbonyl group would be easily achieved. In the event, treatment of (+)-**6** with 1,2-ethanethiol (1 eq, BF_3-Et_2O 0.1 eq, AcOH, 60 °C, 10 h) afforded the requisite (+)-**9** in 70 % yield. Finally, removal of the thioketal moiety was performed using excess Raney Ni (MeOH, 20 °C, 1 h) to furnish the desired β-keto ester (+)-**2**, $[\alpha]_D$ = +15.0 (c = 1.2, $CHCl_3$) [8], in 87 % yield.

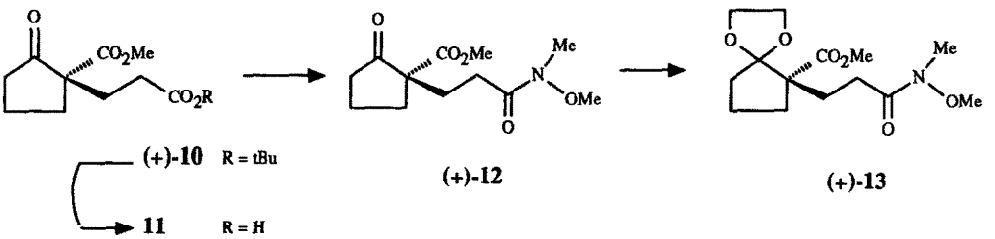


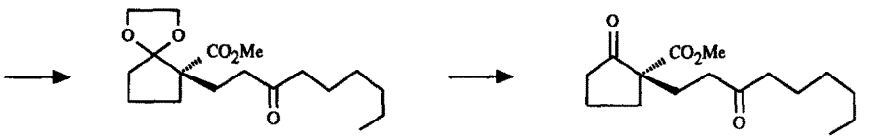
(+)-3 7 8 (+)-6 (+)-9

Scheme 3

The route described above to β-keto ester (+)-**2** had the merit of conciseness but was not entirely satisfying in terms of enantioselectivity. In the hope of increasing the optical purity of (+)-**2** we came to favor a somewhat less direct route wherein the starting material would be the β-keto ester (+)-**10** [3]. Such a strategy involved the elongation of the side chain to provide the proper number of carbon atoms. Toward this end, attention was directed to the synthesis of amide **13**. The expectation was that reaction of *n*hexylmagnesium bromide onto **13** would occur chemoselectively at the amide center [9]. Transformation of β-keto ester (+)-**10** (85 % ee) to **13** was accomplished as follows : Brief exposure of (+)-**10** to $TiCl_4$ (1 eq, CH_2Cl_2, 0 °C, 10 min then H_2O) effected the chemoselective hydrolysis of the *tert*-butylester group to give the acid **11** in 90 % yield. Reaction of the latter compound with 1 eq of 0,N-dimethylhydroxylamine hydrochloride (1.3 eq NEt_3,

1.05 eq DCC, c.a DMPA, CH_2Cl_2, 0 °C to RT) afforded the amide (+)-**12** as a colorless oil $[\alpha]_D$ = +16.8 (c = 6, EtOH), which solidified upon standing in the cold (mp = 47 °C). Recrystallization (ether, -40 °C) gave a white solid (mp = 52 °C) and led to optical purity enhancement (ee ≥ 95 % *vide infra*) as evidenced by the optical rotation, $[\alpha]_D$ = +19.6 (c = 6, EtOH). Protection of the carbonyl group in (+)-**12** was best accomplished in two steps. Reaction of **12** with trimethyl *ortho*formate absorbed on the Montmorillonite clay K 10 (CCl_4, 20 °C, 10 h) [10] led to a mixture of the corresponding acetal and enol ether which, without purification, was reacted with 1,2-ethanediol (5 eq, PhH, reflux, 3 h) to provide the key intermediate [11] (+)-**13** in 80 % yield. In line with our assumption treatment of (+)-**13** with *n* hexylmagnesium bromide (3 eq of a 2 M solution in ether, 0 ° to 20 °C, 1 h) resulted in the selective formation of (+)-**14** [12] in 70 % yield. Exposure of (+)-**14** to dilute acid (HCl 2 N, THF : MeOH 4:1, reflux, 10 h) afforded (+)-**6** [12] in 90 % yield. Finally, transformation of (+)-**6** as previously reported (*vide supra*) afforded, via the thioketal (+)-**9** [12] the target β-keto ester (+)-**2**, $[\alpha]_D$ = +21.4 (c = 1.2, $CHCl_3$) [8], in high enantiomeric excess (≥ 95 % according to NMR analysis in the presence of Eu $(hfc)_3$).





Scheme 4

In conclusion, an efficient asymmetric synthesis of (+)-**2**, a known precursor of the antibiotic (−)-malyngolide **1** has been described in a few steps.

References and Notes

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2 Total asymmetric synthesis : a) Sakito, Y. ; Tanaka, S. ; Asami, M. ; Mukaiyama, T. *Chemistry Letters*, **1980**, 1223. b) Kogure, T. ; Eliel, E.L. *J. Org. Chem.*, **1984**, *49*, 578. c) Giese, B. ; Rupaner, R. *Liebigs Ann. Chem.*, **1987**, 231. d) Sato, T. ; Maeno, H. ; Noro, T. ; Fujisawa, T. *Chemistry Letters*, **1988**, 3739. e) Suemune, H. ; Harabe, T. ; Xie, Z.F. ; Sakai, K. *Chem. Pharm. Bull.*, **1988**, *36*, 4337. f) Honda, T. ; Imai, M. ; Keino, K. ; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2677. g) Ichimoto, I. ; Machiya, K. ; Kirihata, M. ; Ueda, H. *Agric. Biol. Chem.*, **1990**, *54*, 657.
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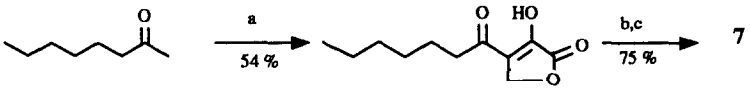
3 Guingant, A. ; Hammami, H. *Tetrahedron Asymmetry*, preceding communication in this issue.

4 All compounds described in this paper were isolated as colorless oils after flash chromatography and bulb to bulb distillation.

5 **6** $[\alpha]_D$ = +12.6 (c = 2.9, EtOH) ; **9** $[\alpha]_D$ = +21.5 (c = 1.6, EtOH).

6 Prepared as follows (see Tanaki, K. ; Okada, M. ; Yamada, M. ; Negoro, K. *J. Org. Chem.* **1982**, *47*, 1200.



a $(CO_2Et)_2$ 1 eq, EtONa 1.15 eq, ether then 30 % aq. HCHO
b NaH 1.15 eq, PhSeCl 1.12 eq, THF, 20 °C. c 20 % $KHCO_3$

7 ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.4 (s, 1H) 5.4 (s, 1H) 2.7 (t, J=7.5 Hz, 2H)

7 The mixture was conveniently separated via flash chromatography (hexane:ethylacetate 6:1) for characterization purpose. Less polar isomer (major) : $[\alpha]_D$ = -177 (c = 1.8, EtOH). *^{1}H NMR* (90 MHz, C_6D_6) δ 4.3 (dd, J=6 Hz, J=4 Hz, 1H), 3.35 (s, 3H). *^{13}C NMR* (20 MHz, $CDCl_3$) δ 215.2, 205.4, 172.2, 135.6, 129.1, 128.7, 127.4, 60.0, 52.5, 46.8, 41.0, 38.0, 35.8, 35.5, 31.6, 28.8, 23.7, 22.5, 19.5, 14.0 ; *IR* (neat) 1745, 1728, 1705 cm^{-1}. More polar isomer (minor) : $[\alpha]_D$ = +148 (c = 1.8, EtOH). *^{1}H NMR* (90 MHz, C_6D_6) δ 4.05 (dd, J=7.5 Hz, J=6 Hz), 3.15 (s, 3H). *^{13}C NMR* (20 MHz, $CDCl_3$) δ 213.3, 205.1, 170.8, 135.8, 129.2, 128.9, 127.3, 60.5, 52.6, 46.8, 41.0, 37.2, 34.7, 33.2, 31.5, 28.8, 24.1, 22.9, 19.3, 14.0 ; *IR* (neat) 1755, 1728, 1705 cm^{-1}.

8 Reported value : $[\alpha]_D$ = +20.9 (c = 1.13, $CHCl_3$) [2d].

9 Nahm, S. ; Weinreb, S. *Tetrahedron Lett.*, **1981**, *22*, 3815.

10 Taylor, E.C. ; Chiang, C.S. *Synthesis*, **1977**, 467.

11 *^{1}H NMR* (90 MHz, $CDCl_3$) δ 3.85 (m, 4H), 3.60 (s, 3H), 3.58 (s, 3H), 3.1 (s, 3H) ; *IR* (neat) 1735, 1660 cm^{-1}.

12 **13** $[\alpha]_D$ = +10.3 (c = 2.2, EtOH) ; **14** $[\alpha]_D$ = +14.0 (c = 4.5, EtOH) ; **6** $[\alpha]_D$ = +16.5 (c = 2.8, EtOH) ; **9** $[\alpha]_D$ = +27.4 (c = 1.5, EtOH).