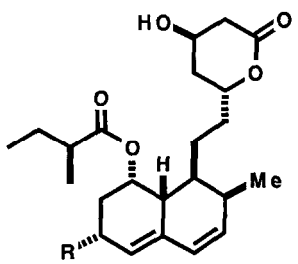
Tetrahedron Letters,Vol.29,No.49 pp 6467-6470,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A FACILE ENTRY TO β,δ-DIKETO AND *syn*-β,δ-DIHYDROXY ESTERS

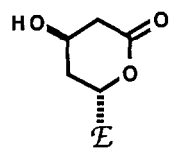
Takeshi Hanamoto and Tamejiro Hiyama*
Sagami Chemical Research Center
4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan

Reaction of N-*methoxy*-N-*methyl amides with the dianions of acetoacetates gives β,δ–diketo esters in yields of synthetic use, and the diketo esters were selectively reduced to* syn-*β,δ–dihydroxy esters, key intermediates of synthetic HMG-CoA reductase inhibitors.*

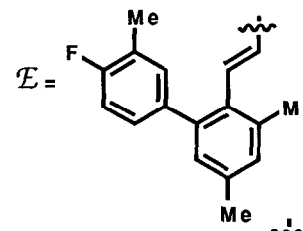
Mevinolin (monakolin K) and compactin (ML-236 B) are highly potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and have been expected to be useful hypocholesterolemic agents.[1] However, the side effects sometimes encountered stimulated search for synthetic congeners like those shown below, all of which contain a β-hydroxy-δ-lactone moiety in common.[2] Thus, new synthetic technologies for construction of the specific structural unit have appeared.[3] Of these, stereoselective reduction of aldols to give *syn*-diols has been shown to be a reliable method.[2b,4] We envisioned that β,δ-diketo esters should be more flexible synthetic intermediates whose stereoselective (asymmetric) reduction provides us with a short-cut way to the target molecules. We report herein an efficient synthesis of the β,δ-diketo esters and their stereoselective *syn*-reduction.[5]

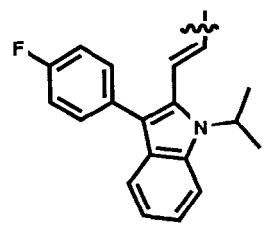


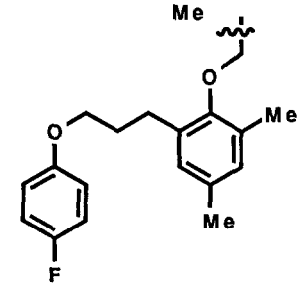
R = Me: mevinolin (monakolin K)
H: compactin (ML-236 B)



Synthetic Analogs

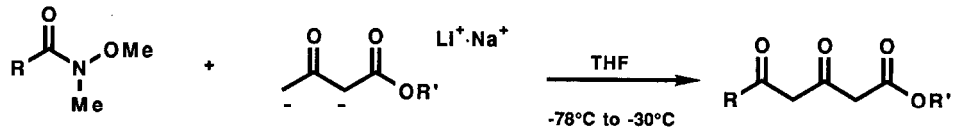






The title β,δ-diketo esters are versatile intermediates for polyketide synthesis, and hence their synthetic methods have been well-studied. By literature survey we concluded that the best approach for our targets would be the one which involves condensation of acid derivatives with dianions of acetoacetates. In order to prepare methyl 3,5-dioxo-7-phenyl-6-heptenoate (**3a"**), we first applied the Yamaguchi's procedure,[6] namely, the reaction of the dianion of methyl acetoacetate with *N,N*-

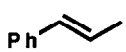
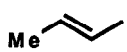
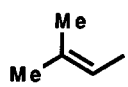
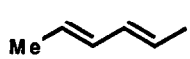
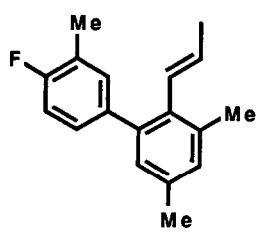
Scheme 1



1 2: R' = *t*Bu, 2': R' = Et, 2'': R' = Me 3

a: R = PhCH=CH, b: R = MeCH=CH, c: R = Me_2C=CH, d: R = MeCH=CH-CH=CH, e: R = 4,6-Me_2-2-(4-F-3-Me-C_6H_3)-C_6H_2CH=CH, f: R = $PhOCH_2$

Table 1 Synthesis of β,δ-Diketo Esters (3) by the Reaction of **1** and **2**[a)]

entry	R		R'		Product (% yield)	
1		**1a**	*t*Bu	**2**	**3a**	49
2		**1a**	Et	**2'**	**3a'**	49
3		**1a**	Me	**2''**	**3a''**	57
4		**1b**	*t*Bu	**2**	**3b**	42
5		**1c**	*t*Bu	**2**	**3c**	90
6		**1d**	*t*Bu	**2**	**3d**	79
7		**1e**	*t*Bu	**2**	**3e**	75
8	$PhOCH_2$	**1f**	*t*Bu	**2**	**3f**	91

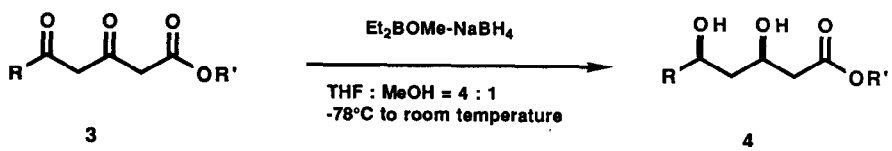
a) All the new compounds gave satisfactory elementary analyses (or high resolution mass spectra) as well as ^{1}H NMR and IR spectra.

dimethylcinnamide. Contrary to our expectation, we obtained a 1 : 2 adduct only in a 57% yield. Possibly conjugate addition of the dianion is followed by the desired condensation. To modify the reactivity of the electrophilic part, we applied cinnamoyl chloride or 1-cinnamoylimidazole to the reaction and observed formation of complex mixture of products or recovery of the acid, respectively. After a lot of unsuccessful experiments we finally employed an *N*-methoxy-*N*-methyl amide[7] (**1a**) as the acid partner. The coupling reaction proceeded smoothly to afford the desired product **3a"** in 57% yield. In addition to the methyl ester (**2"**), ethyl and *t*-butyl ester (**2'** and **2**, respectively) of acetoacetic acid could be used. Results obtained with various *N*-methoxy-*N*-methyl amides are summarized in Table 1. It is apparent that the condensation reaction reported herein is highly effective for the synthesis of (poly)ene diketo esters. No trace of conjugate addition product was detected. For a substrate without a double bond, the reaction is almost quantitative (run 8). Only one failure was the reaction of PhC≡CCON(Me)OMe with **2**, wherein complex mixture of products resulted.

Typical experimental procedures are represented by the synthesis of **3"a**. N-Methoxy-N-methylcinnamide (**1a**, 8.12 g, 76% yield) was prepared by the reaction of cinnamoyl chloride (9.35 g, 56 mmol) with *N,O*-dimethylhydroxylamine hydrochloride (5.76 g, 59 mmol), and pyridine (10.5 ml, 0.13 mol) at 0 °C to room temperature for 2 h.[7] Condensation of **1a** with **2"** was carried out as follows. Under an argon atmosphere, methyl acetoacetate (12.1 ml, 0.113 mol) was added to a stirred slurry of sodium hydride (60% in oil, 4.5 g, 0.113 mol) in THF (250 ml) at 0 °C. The mixture was stirred for 10 min before cooling at -10 °C. A 1.48 M hexane solution of butyllithium (76 ml, 0.113 mol) was added to this solution, and the resulting mixture was stirred for 10 min and then cooled at -78 °C. The amide **1a** (7.2 g, 38 mmol) was added to the dianion solution and the whole was stirred for 30 min at -78 to -30 °C before quenching with dil hydrochloric acid. Workup followed by chromatographic purification gave **3a"** (5.3 g, 57% yield). Mp 52-53 °C. IR (KBr) 3420, 1740, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45 (s, 2 H), 3.76 (s, 3 H), 5.75 (s, 1 H), 6.47 (d, 1 H, J = 15.8 Hz), 7.25-7.70 (m, 5 H), 7.63 (d, 1 H, J = 15.8 Hz), 14.83 (br s, 1 H); MS *m/z* 246 (M^+). Found: C, 68.22; H, 5.93%. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%.

The second problem of our approach is a stereoselective *syn*-reduction of **3**. The recently established chelation controlled hydride reduction[4] might be applicable. However, we reasoned that the presence of a protonic solvent should be needed to do the reduction in one-step[8] and soon found that the modification of the procedure recently disclosed by Prasad[2b] met our criteria. Thus, **3** was reduced with a reagent system which consists of diethyl(methoxy)borane and sodium borohydride in a 4 : 1 mixture of THF and methanol to afford **4** with high diastereoselectivities (usually >95 : 5) and in good yields. No conjugate reduction was observed. Three examples are shown in Table 2. The *syn*-diol **4e** was successfully hydrolyzed and lactonized to afford the racemic derivative of one of the synthetic analogs (*vide supra*).[2a]

Scheme 2



3 **4**

Experimental details follow. Under an argon atmosphere, diethyl(methoxy)borane (0.015 ml, 0.112 mmol) was added to the solution of **3"a** (23 mg, 0.093 mmol) in THF (1 ml) and methanol (0.25 ml) at -78 °C. The mixture was once warmed to room temperature and cooled again at -78 °C, treated with

sodium borohydride (18 mg, 0.47 mmol), gradually warmed to room temperature and then quenched with acetic acid (3 ml). Workup and purification by preparative TLC gave **4a"** (20 mg, 86% yield).[2b] ^{1}H NMR ($CDCl_3$) absorptions at δ 6.21 (dd, J = 15.9, 6.5 Hz, 1 H) and 6.61 (d, J = 15.9 Hz, 1 H) are characteristic of the *syn*-diol structure, and no trace of absorptions were observed at δ 6.26 (dd, J = 15.9, 5.9 Hz, 1 H), 6.64 (d, J = 15.9 Hz, 1 H) attributable to the *anti*-diol.

The two-step procedure disclosed herein for the synthesis of *syn*-β,δ-dihydroxy esters has an advantage that the chiral centers may be introduced in one step by asymmetric reduction[9] at the late stage of the synthesis. Studies along this line are in progress in our Laboratories.

Table 2 *syn*-Selective Reduction of the Diketo Esters **3**[a)]

Starting Material	Product	(% yield)	syn : anti[b)]
3a"	**4a"**	86	>95 : 5
3e	**4e**	68	>95 : 5
3f	**4f**	94	>95 : 5

a) All the new compounds gave satisfactory analytical and spectral data.
b) Determined by the ratio of the intensities of the relevant ^{1}H NMR (400 MHz) signals.

References and Notes

1 Endo, A. *J. Med. Chem.* **1985**, *28*, 401.
2 (a) Willard, A. K.; Novello, F. C.; Hoffman, W. F.; Cragoe, E. J. US Patent 4,375,475 (1983). (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**,*28*,155; Chen, K.-M.; Gunderson, K. G.; Hardtmann, G.E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923. (c) Günther, W.; Ernold, G.; Gerhard, B.; Hans-Hermann, L. Deutsches Patent DE 3530798 A1. (d) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Kesseler, K.; Wess, G.; Schubert, W.; Granzer, E.; Kerekjarto, B.V.; Krause, R. *Tetrahedron Lett.* **1988**, *29*, 929.
3 (a) Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.***1987**, *28*, 1385 and references cited therein. (b) Heathcock, C. H.; Hadley, C. R.; Rosen, T. Theisen, P. D.; Hecker, S. J.; *J. Med. Chem.* **1987**, *30*, 1858. (c) Johnson, W. S.; Kelson, A. B.; Elliott, J. D. *Tetrahedron Lett.* **1988**, *29*, 3757.
4 (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (b) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803. (c) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009.
5 Condensation of nitriles with the dianions **2-2"** in the presence of zinc ion is claimed in a patent. Verhoeven, T. R.; McNamara, J. M. Eur. Pat. Appl. EP 204,287. However, we found it hard to reproduce the results.
6 Yamaguchi, M.; Shibato, K.; Hirao, I. *Chem. Lett.* **1985**, 1145.
7 Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
8 ^{1}H NMR disclosed that the δ–carbonyl groups of **3a-f** are enolized. Our design of the reaction is following. An exchange reaction between the enol moiety and diethylmethoxyborane should afford a vinyloxyborane intermediate, the β–carbonyl group of which would be reduced first to give, after protonation, a β–hydroxy ketone intermediate requisit to the *syn*-reduction.
9 By using chiral dialkyl(methoxy)borane, the asymmetric reduction is feasible. We have observed that a methoxyborane derived from (*S*)-(-)-limonene certainly gives *syn*-diols (selectivity >95%) albeit of only 8% ee.

(Received in Japan 6 October 1988)