Tetrahedron Letters, Vol.31, No.51, pp 7513-7516, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

TOTAL SYNTHESIS OF THE ESTERASE INHIBITOR (±)-EBELACTONE A USING AN ALDOL-CLAISEN STRATEGY.

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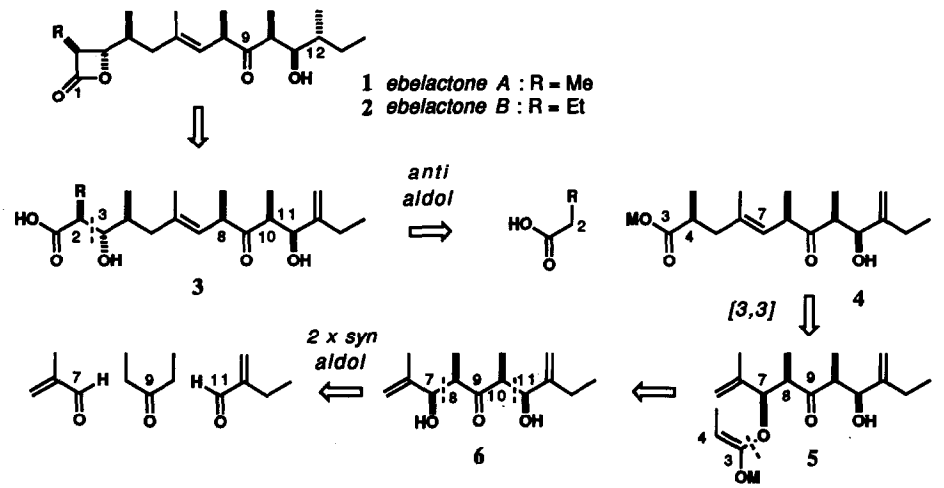
Summary: The β-lactone (±)-ebelactone A has been prepared in 12 steps from diethylketone (9% overall yield) using a series of three boron enolate aldol reactions coupled with the Ireland ester enolate Claisen rearrangement, **10** → **11**.

The ebelactones are a small group of β-lactone enzyme inhibitors, which were isolated from a cultured strain of soil actinomycetes (MG7-G1 related to *Streptomyces aburaviensis*) by the Umezawa group in 1980.[1] They act as potent inhibitors of esterases, lipases and *N*-formylmethionine aminopeptidases located on the cellular membrane of various kinds of animal cells, thus producing enhanced immune responses.[1a] The ebelactones are also found to inhibit cutinases produced by fungal plant pathogens and may have use as plant protectants.[2] The structure of ebelactone A has been determined by X-ray crystallography to be as shown in **1**,[1b] while ebelactone B was proposed from spectral comparisons to be the one carbon homologue **2**. Structurally, ebelactones A and B show close similarities to the macrolide antibiotics and their related polyketide biosynthetic origin has been demonstrated.[3] In considering synthetic approaches to the ebelactones, we wished to develop a short and flexible route which would also allow ready access to structural analogues. We now report the first total synthesis of (±)-ebelactone A and describe a versatile aldol-Claisen synthetic strategy for this general class of β-lactone enzyme inhibitors.

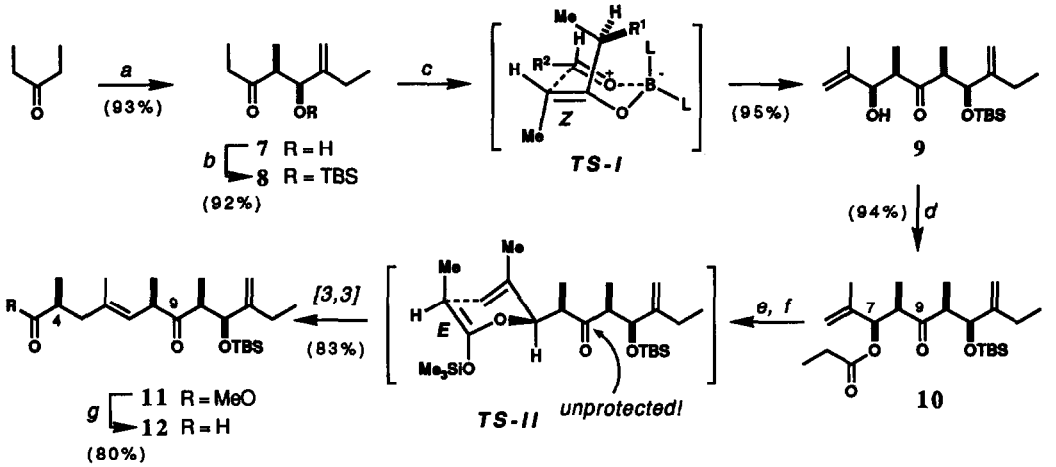


Scheme 1

Our retrosynthetic analysis for the ebelactones, as shown in **Scheme 1**, relies on a series of three aldol reactions to control the stereochemistry at C_2, C_3, C_8, C_{10}, and C_{11} in **3**. The remote C_4 stereocentre, together with the *E* double bond geometry, were planned to arise from an Ireland-Claisen rearrangement,[4] **4** ⇒ **5** (*ideally without protecting the C_9 ketone*). This would serve to relay 1,2-*syn* into 1,5-*syn* relative stereochemistry.[5] From our earlier work on the synthesis of the ansa chain of rifamycin S, the required ketone precursor **6** should

in turn be accessible with the correct all-*syn* stereochemistry by boron enolate aldol chemistry.[6] While an asymmetric synthesis should be possible using chiral boron enolates,[7] we chose to first explore this aldol-Claisen approach in the racemic series.

The sequential aldol reactions of diethylketone with methacrolein and 2-ethyl acrolein were performed using *Z* dialkylboron enolates with >95% diastereoselectivity in each step (**Scheme 2**). The first aldol reaction with 2-ethyl acrolein using $^{n}Bu_2BOTf/^{i}Pr_2NEt$ gave the *syn* adduct **7**,[8,9] which was protected as its TBS ether **8**. Enolisation with 9-BBNOTf/Et_3N and addition to methacrolein gave the all-*syn* adduct **9**, *via* the preferred chair transition state ***TS-I***,[6] in 81% overall yield. The propionate ester was then obtained, **9** → **10**, by use of propionic anhydride and catalytic DMAP (Et_3N, CH_2Cl_2, 20°C, 2 h; 94%).

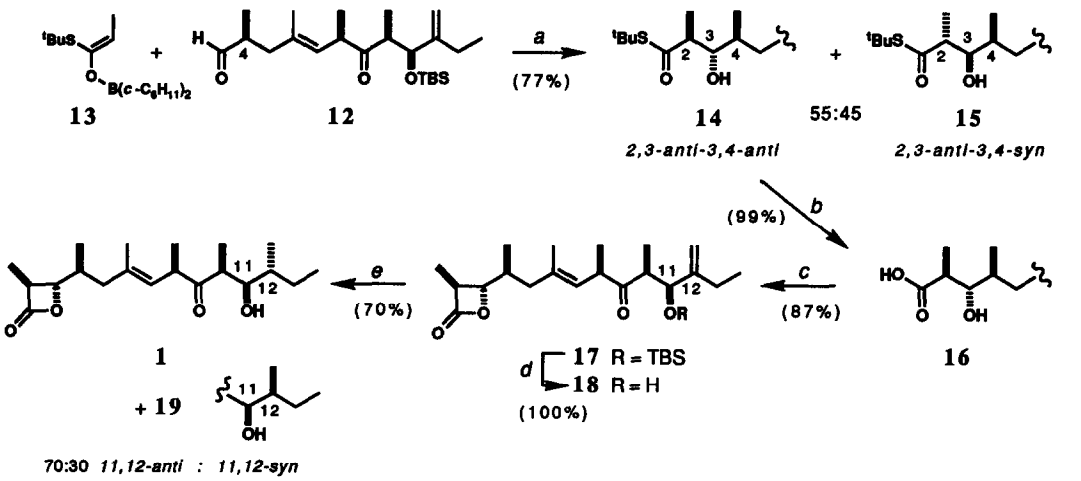


Scheme 2 (*a*) $^{n}Bu_2BOTf$, $^{i}Pr_2NEt$, CH_2Cl_2, -78°C, 3 h; H_2=C(Et)CHO, -78 → 0 °C, 16 h; H_2O_2, MeOH-pH 7 buffer; (*b*) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78°C, 1 h; (*c*) 9-BBNOTf, Et_3N, -78°C, 4 h; H_2=C(Me)CHO, -78 → -20 °C, 16 h, H_2O_2, MeOH-pH 7 buffer; (*d*) $(EtCO)_2O$, cat. DMAP, Et_3N, CH_2Cl_2, 0 → 20 °C, 2 h; (*e*) Me_3SiCl, Et_3N, THF, LDA, -78 °C, 1 h; 20 °C, 1 h; 60 °C, 2 h; aq. 1% HCl; (*f*) CH_2N_2, Et_2O, 0 °C; (*g*) DIBAL, Et_2O, -98 °C, 20 min; MeOH.

The critical Ireland ester enolate Claisen rearrangement could be performed smoothly on **10** under carefully defined reaction conditions without any interference by the ketone carbonyl group. A solution of LDA (1.6 equiv) in hexane was added to a stirred solution of **10** in THF containing premixed[10] Me_3SiCl (5 equiv) and Et_3N (4.5 equiv) at -78 °C. Under these modified Corey-Gross conditions,[11] the kinetically generated *E* ester enolate[12] was rapidly trapped *in situ* preventing any deleterious proton transfers or aldol additions (intra- or intermolecularly). The solution of ketene silyl acetal so formed was then warmed to 20 °C for 1 h then 60 °C for 2 h, followed on cooling by extraction into pentane and washing with 1% aq. HCl. The Claisen rearrangement product was isolated as the methyl ester **11** (CH_2N_2) with >95% diastereoselectivity[12,13] in 83% yield. Subsequent reaction of **11** with DIBAL at -98°C (Et_2O, 20 min) selectively reduced the ester group to the aldehyde, giving **12**[12] in 80% yield. Presumably the ketone is reduced more slowly here due to its hindered environment.[14]

Since the ebelactones have 2,3-*anti*-3,4-*anti* stereochemistry, the final aldol reaction of the racemic synthesis relied on the α-chiral aldehyde **12** showing low Cram (Felkin-Anh) selectivity with an appropriate *E* enol borinate. In practice (**Scheme 3**), the aldol addition of the *E* dicyclohexylenol borinate **13** of *tert*-butylthiopropionate[15] (generated by enolisation with $(c\text{-}C_6H_{11})_2BCl/Et_3N$)[16] with **12** in pentane gave the required 3,4-*anti* adduct **14**[13] together with the 3,4-*syn* isomer **15** in a ratio of 55:45 (77%).[17] These were

separated (HPLC) and individually taken through the final steps of the synthesis. Thioester hydrolysis in **14** proceeded cleanly without any epimerisation using LiOOH in THF to give the carboxylic acid **16** (99%), which was then lactonised to give the β-lactone **17**[13] in 87% yield by portionwise treatment with $PhSO_2Cl$ in pyridine.[18] After deprotection with HF/MeCN (100%), the allyl alcohol **18** was submitted to Rh(I) catalysed homogeneous hydrogenation. Use of $(Ph_3P)_3RhCl$ (1 atm. H_2, PhH), led to an *anti:syn* ratio of 70:30 in 70% yield (R_f = 0.42 and 0.35 in Et_2O/CH_2Cl_2, 1:9).[19] The higher R_f, *anti* product **1** was identical (400 MHz ^1H NMR, 100 MHz ^{13}C NMR, IR, CI-MS, TLC) with an authentic sample[20] of ebelactone A.



Scheme 3 (*a*) ^{t}BuSCOEt, $(c\text{-}C_6H_{11})_2BCl$, Et_3N, pentane, 0 °C, 1.5 h (→ **13**); **12**, -78 → -4 °C, 16 h; H_2O_2, MeOH-pH 7 buffer; (*b*) 30% H_2O_2, LiOH, aq. THF, 0 → 20 °C, 20 h; Na_2SO_3; (*c*) $PhSO_2Cl$, pyridine, -20 °C, 16 h; (*d*) 40% aq. HF, MeCN, 20 °C, 2 h; (*e*) H_2, $(Ph_3P)_3RhCl$, PhH, 20 °C, 2 h.

The above synthetic route should be easily adaptable to provide an enantioselective approach to the ebelactones and analogues. The other merits of the present synthesis are (*i*) brevity (12 steps from diethylketone), (*ii*) a good overall yield (9%), and (*iii*) the minimum use of protecting groups.

Acknowledgement: We thank the SERC for support (Studentship to ANH). IP thanks the Royal Society of Chemistry for a Hickinbottom Research Fellowship.

References and Notes

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9. All new compounds gave spectroscopic data in agreement with the assigned structures.

10. A clear reagent solution was prepared by mixing Me_3SiCl and Et_3N and removing the precipated $Et_3N.HCl$ by centrifugation.

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12. While a single isomer was apparent from examination of the ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra,[14] the 4,8-*syn* and *anti* isomers of **11** might be expected to have very similar and possibly coincidental spectra (*cf* ref 5b). However, the subsequent DIBAL reduction step produced only one detectable isomer of the aldehyde **12**, since mild base treatment led to a roughly equimolar ratio of the two C_4 epimers with slightly different ^1H NMR spectra. This suggests that the *E* ester enolate was obtained with high stereoselectivity and [3,3] rearrangement took place preferentially *via* the normal chair transition state, *i.e.* ***TS-II*** in **Scheme 2.**

13. **11** had ^1H NMR δ ($CDCl_3$, 400 MHz) 5.03 (1H, dd, *J* = 9.8, 1.1 Hz), 4.90 (1H, s), 4.76 (1H, d, *J* = 1.6 Hz), 4.29 (1H, d, *J* = 8.1 Hz), 3.66 (3H, s), 3.40 (1H, dq, *J* = 6.9, 9.8 Hz), 2.83 (1H, dq, *J* = 8.1, 7.0 Hz), 2.60 (1H, dqn, *J* = 8.6, 6.7 Hz), 2.40 (1H, dd, *J* =13.7, 6.7 Hz), 2.07 (1H, m), 2.02 (1H, dd, *J* = 13.7, 8.6 Hz), 1.90 (1H, m), 1.65 (3H, d, *J* = 1.1 Hz), 1.09 (3H, d, *J* = 6.9 Hz), 1.07 (3H, d, *J* = 7.0 Hz), 1.05 (3H, d, *J* = 6.7 Hz), 1.00 (3H, t, *J* =7.4 Hz), 0.87 (9H, s), 0.04 (3H, s), -0.03 (3H, s); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 213.7, 176.8, 151.3, 134.4, 126.4, 110.7, 77.5, 51.6, 49.8, 45.8, 43.4, 37.5, 25.8, 22.5, 18.2, 16.6, 16.3, 16.1, 14.3, 11.5, -4.5, -5.1; HRMS (CI, NH_3) calc for $C_{24}H_{45}O_4Si$ (M^++H) 425.3087, found 425.3087. **14** had ^1H NMR δ ($CDCl_3$, 400 MHz) 4.96 (1H, d, *J* = 9.7 Hz), 4.90 (1H, s), 4.75 (1H, d, *J* = 1.4 Hz), 4.30 (1H, d, *J* = 8.3 Hz), 3.43 (1H, dq, *J* = 9.7, 6.9 Hz), 3.31 (1H, t, *J* = 5.7 Hz), 2.85 (1H, qn, *J* = 7.3 Hz), 2.81 (1H, dq, *J* = 8.3, 6.8 Hz), 2.43 (1H, d, *J* = 11.4 Hz), 2.07 (1H, m), 1.90 (1H, m), 1.70 (1H, m), 1.64 (1H, d, *J* = 11.4 Hz), 1.63 (3H, s), 1.47 (9H, s), 1.28 (3H, d, *J* = 7.3 Hz), 1.10 (3H, d, *J* = 6.9 Hz), 1.05 (3H, d, *J* = 6.8 Hz), 1.00 (3H, t, *J* = 7.4 Hz), 0.88 (9H, s), 0.82 (3H, d, *J* = 6.2 Hz), 0.04 (3H, s), -0.03 (3H, s). **17** had ^1H NMR δ ($CDCl_3$, 400 MHz) 5.05 (1H, d, *J* = 9.8 Hz), 4.90 (1H, s), 4.77 (1H, s), 4.29 (1H, d, *J* = 8.1 Hz), 3.87 (1H, dd, *J* = 8.5, 4.2 Hz), 3.44 (1H, dq, *J* = 9.8, 6.8 Hz), 3.28 (1H, dq, *J* = 7.5, 4.2 Hz), 2.85 (1H, dq, *J* = 8.1, 6.9 Hz), 2.34 (1H, dd, *J* = 13.2, 4.0 Hz), 2.08 (1H, m), 1.96 (1H, m), 1.91 (1H, m), 1.74 (1H, dd, *J* = 13.2, 10.1 Hz), 1.65 (3H, s), 1.41 (3H, d, *J* = 7.5 Hz), 1.15 (3H, d, *J* = 6.8 Hz), 1.11 (3H, d, *J* = 6.9 Hz), 1.00 (3H, t, *J* = 7.4 Hz), 0.88 (9H, s), 0.83 (3H, d, *J* = 6.7 Hz), 0.04 (3H, s), -0.03 (3H, s); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 213.7, 171.8, 151.5, 133.9, 126.8, 110.6, 82.9, 77.6, 50.0, 48.9, 45.6, 42.7, 35.3, 25.6, 22.4, 18.2, 16.8, 16.1, 14.3, 13.2, 12.8, 11.5, -4.6, -5.1; HRMS (CI, NH_3) calc for $C_{26}H_{47}O_4Si$ (M^++H) 451.3244, found 451.3244.

14. Varying amounts (5-15%) of ketone reduction products were also obtained from the DIBAL reaction of **11**.

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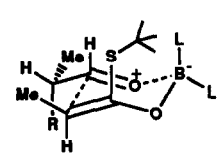
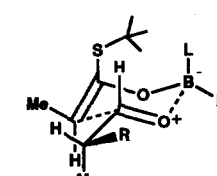
16. This reagent system leads to a high level of *anti* selectivity in the aldol reactions of *tert*-butylthiopropionate, *e.g.* >99:1 *anti*:*syn* for addition to isobutyraldehyde (*cf* ref 15). Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

17. The same reaction in dichloromethane favoured formation of the Cram product **15** (2:1 ratio of **15**:**14**). A fine balance must exist between ***TS-III*** and ***TS-IV*** for aldehyde **13**, *i.e.* it shows a low level of intrinsic π-face selectivity. This will be useful when using a *chiral* enolate in combination with *non-racemic* **13**.



transition state leading to the desired 3,4-*anti* isomer **14**



Felkin - Anh transition state leading to the 3,4-*syn* isomer **15**

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19. We hope to improve on the *anti* stereoselectivity of this last step by using allylic hydroxyl directed hydrogenation with cationic Rh(I) catalysts, see: Brown, J. M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 190.

20. Sigma Chemical Co. Ltd. (E 0761).

(Received in UK 25 October 1990)