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Ti(III)-induced radical cyclization. A stereoselective entry to the perhydrobenzo[*e*]indene unit of new protein farnesyltransferase inhibitors, andrastins A–D

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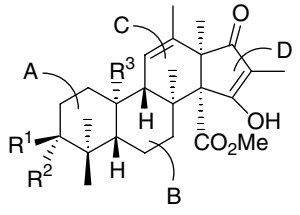
Abstract—An efficient approach for the synthesis of a fully functionalized perhydrobenzo[*e*]indene, the BCD ring system of andrastins A–D, is described. The synthesis commences from (±)-Wieland–Miescher ketone and features a Ti(III)-induced radical cyclization as the central step.

Andrastins A (**1a**), B (**1b**), C (**1c**), and D (**1d**), discovered in the cultured broth of *Penicillium* sp. FO-3929 by Ōmura and co-workers in 1996, are novel protein farnesyltransferase inhibitors.[1] Since farnesylation is essential for the transforming activity of mutated Ras proteins, andrastins (**1**) are expected as promising antitumor agents.[2] The novel tetracyclic carbon skeletons of these meroterpenoids (**1**) incorporate six or seven stereogenic centers and an angularly disubstituted perhydrobenzo[*e*]indene moiety, which comprises the B, C and D rings (Fig. 1).



Andrastin A (**1a**): R^1=OAc, R^2=H, R^3=CHO
Andrastin B (**1b**): R^1=OAc, R^2=H, R^3=CH_2OH
Andrastin C (**1c**): R^1=OAc, R^2=H, R^3=Me
Andrastin D (**1d**): R^1=R^2=O, R^3=CHO

Figure 1. Structures of andrastins A–D (**1a**–**d**).

Although their unusual structures and biological activities have made them the subject of intense synthetic interest, the total syntheses of andrastins (**1**) have not yet been reported probably due to their structural complexity. Herein, we report a stereoselective strategy for the synthesis of andrastins (**1**) that features the use of a Ti(III)-induced radical cyclization to assemble the perhydrobenzo[*e*]indene substructure.

The synthesis begins with ketone **2**, which is conveniently available on a large scale from (±)-Wieland–Miescher ketone.[3] Methylation of **2** proceeded in excellent yield (92%) to afford **3**, which was converted to enol silane **4** in 90% yield. The palladium-catalyzed modified Ito–Saegusa reaction[4] was performed on **4** to give enone **5** (70%). Reaction of **5** with (benzyloxymethyl)tributylstannane[5] in the presence of butyllithium (−78 °C) afforded a high yield of alcohol **6** as a mixture of diastereoisomers. Oxidation of **6** with PCC in the presence of NaOAc provided enone **7**,[6] which was subjected to DIBAH reduction to furnish allylic alcohol **8** in 92% yield as a separable 4.4:1 mixture in which the α-oriented hydroxyl group was predominant (Scheme 1).

The inversion of hydroxyl group in **8** under Mitsunobu reaction conditions[7] [*N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD), *p*-methoxybenzoic acid, PBu_3, C_6H_6, 60 °C; K_2CO_3, MeOH] resulted in the formation of alcohol **9** (86% for two steps).

The stereochemistry of **9** was finally established by transformation into acetate **16**. Claisen rearrangement

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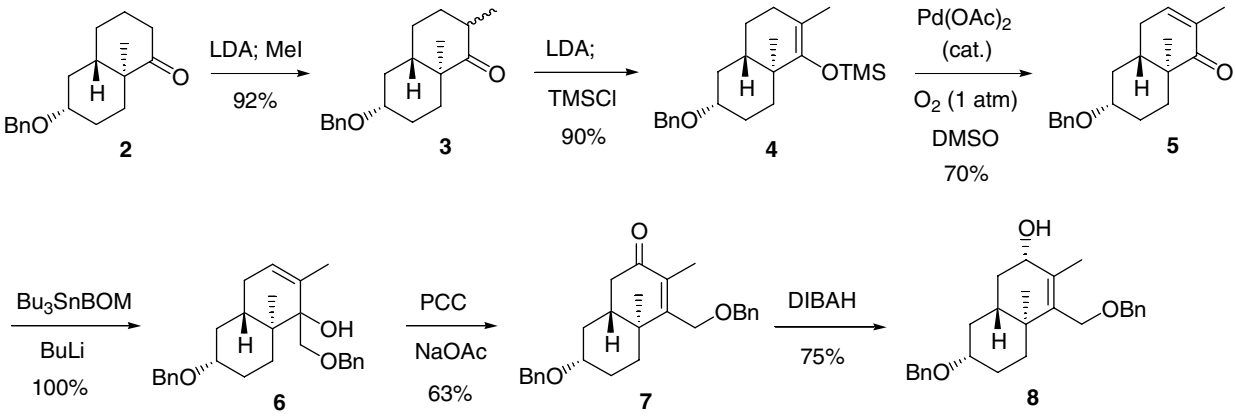
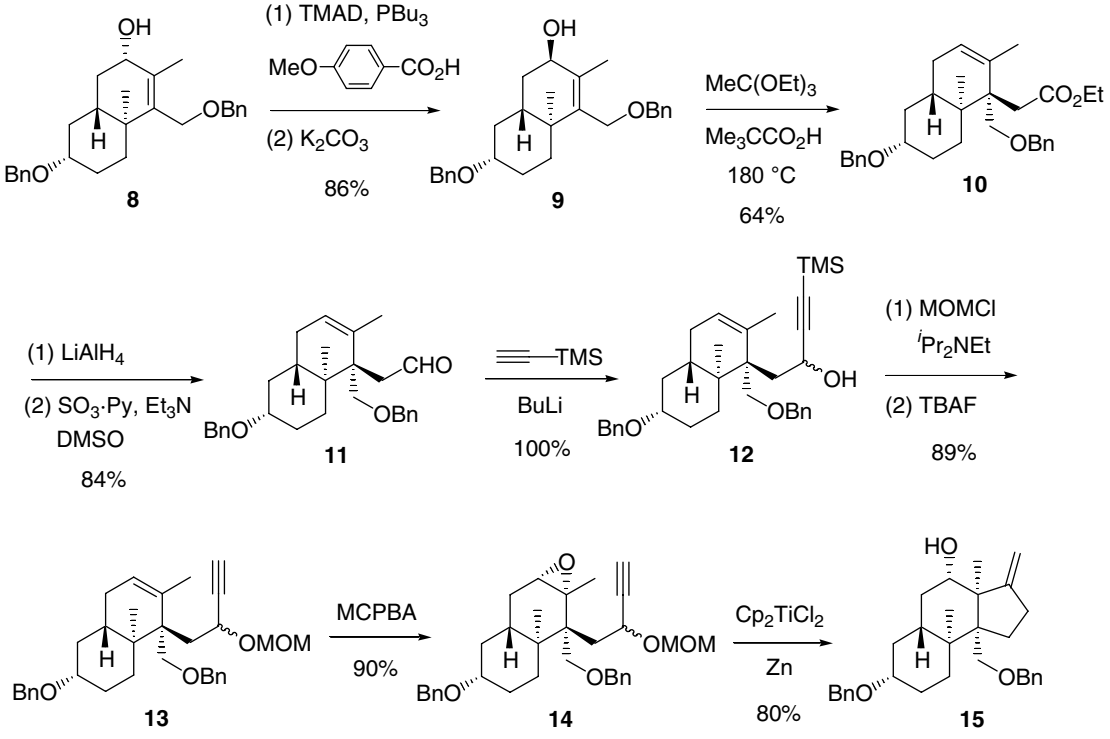


Scheme 1.

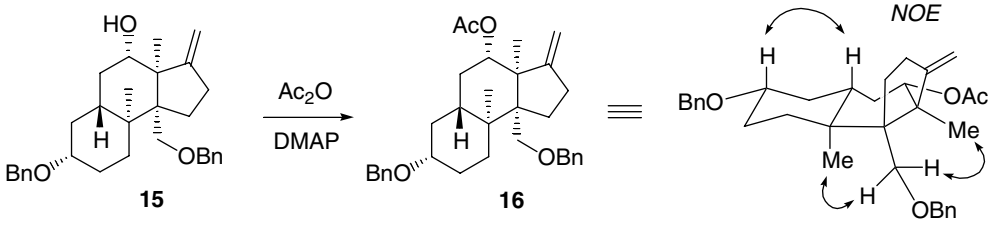
of **9** with triethyl orthoacetate was conducted in the presence of pivalic acid at 180 °C in a sealed tube to lead to ester **10** in 64% yield. Reduction of **10** with $LiAlH_4$ followed by Parikh oxidation provided aldehyde **11** in 84% overall yield. Treatment of **11** with lithium (trimethylsilyl) acetylide afforded an essentially quantitative yield of a mixture of **12** in a ratio of 1:1. Sequential etherification of **12** with chloromethyl methyl ether and desilylation gave rise to acetylene **13** in good overall yield. Finally, regio- and stereoselective epoxidation of **13** with *m*-chloroperbenzoic acid proceeded without incident (90%). With the diastereoselective synthesis of epoxide **14** realized, the stage was now set for Ti(III)-induced radical cyclization.[8] To a stirred solution of Cp_2TiCl, in situ prepared from Cp_2TiCl_2 and zinc in THF, was added dropwise a solution of **14** at room temperature to generate perhydrobenzo[*e*]indene **15** in 80% yield. Interestingly, the methoxymethyl ether group of **14** was removed under such reaction conditions.[9] Details of the reaction mechanism are the subject for future study (Scheme 2).

In order to determine the stereochemistry of the cyclization product **15**, which was transformed into the corresponding acetate **16**. Analyses of the ^1H–^1H COSY experiments of **16** enabled the assignment of all protons. In addition, the relative stereochemistry was established on the basis of NOESY correlations as described in Scheme 3.

In conclusion, we have developed a stereoselective process to construct highly functionalized



Scheme 2.



Scheme 3.

perhydrobenzo[*e*]indene derivative, potential synthon for the synthesis of andrastins, by means of Ti(III)-induced radical cyclization.

Acknowledgements

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6. Selected spectral data are given. Compound **7**: IR (neat, cm^{-1}) 3030, 2936, 2862; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (10H, m), 4.59–4.48 (4H, m), 4.15 (1H, d, $J = 10.0$ Hz), 4.09 (1H, d, $J = 10.0$ Hz), 3.41–3.36 (1H, m), 2.42–2.22 (2H, m), 2.05–1.81 (4H, m), 1.80 (3H, s), 1.69–1.39 (3H, m), 1.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 159.2, 138.6, 137.6, 134.1, 128.4, 128.30, 128.28, 127.8, 127.5, 127.43, 127.41, 73.3, 70.1, 66.2, 40.8, 40.2, 38.5, 33.8, 33.4, 28.0, 16.6, 11.5; LRMS *m/z*: 404 (M^+); HRMS calcd for $C_{27}H_{32}O_3$ (M^+) 404.2351, found: 404.2353. Compound **9**: IR (neat, cm^{-1}) 3420, 2932, 2862; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (10H, m), 4.57 (1H, d, $J = 11.7$ Hz), 4.53 (1H, d, $J = 11.7$ Hz), 4.51 (1H, d, $J = 12.0$ Hz), 4.46 (1H, d, $J = 12.0$ Hz), 3.98 (1H, d, $J = 10.3$ Hz), 3.89 (1H, br s), 3.89 (1H, d, $J = 10.3$ Hz), 3.45–3.35 (1H, m), 2.02–1.94 (1H, m), 1.84–1.70 (4H, m), 1.81 (3H, s), 1.70–1.20 (5H, m), 0.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 138.9, 138.1, 133.9, 128.3, 127.9, 127.6, 127.5, 127.3, 77.6, 72.9, 70.0, 69.6, 65.8, 37.6, 35.7, 34.9, 34.2, 33.9, 28.2, 17.3, 17.0; LRMS *m/z*: 406 (M^+); HRMS calcd for $C_{27}H_{34}O_3$ (M^+) 406.2508, found: 406.2505. Compound **10**: IR (neat, cm^{-1}) 2930, 2866; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (10H, m), 5.45–5.41 (1H, m), 4.53 (2H, s), 4.48–4.39 (2H, m), 4.08–3.90 (2H, m), 3.66–3.60 (2H, m), 3.34–3.24 (1H, m), 2.58 (1H, d, $J = 13.6$ Hz), 2.48 (1H, d, $J = 13.6$ Hz), 2.04–1.90 (2H, m), 1.82 (2H, d, $J = 12.4$ Hz), 1.68 (3H, s), 1.67–1.10 (8H, m), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 139.0, 138.4, 135.2, 128.19, 128.16, 128.1, 127.4, 127.2, 127.1, 124.2, 77.0, 73.2, 72.9, 69.7, 60.0, 49.0, 38.7, 37.3, 35.3, 33.9, 31.8, 30.5, 28.2, 21.1, 14.1, 14.0; LRMS *m/z*: 476 (M^+); HRMS calcd for $C_{31}H_{40}O_4$ (M^+) 476.2927, found: 476.2907. Compound **16**: IR (neat, cm^{-1}) 2934, 2864, 1738; ^1H NMR (600 MHz, C_6D_6) δ 7.37–7.06 (10H, m), 4.92 (1H, t, $J = 2.4$ Hz), 4.90 (1H, t, $J = 2.4$ Hz), 4.80 (1H, t, $J = 2.4$ Hz), 4.41 (2H, s), 4.21 (1H, d, $J = 12.0$ Hz), 4.14 (1H, d, $J = 12.0$ Hz), 3.48 (1H, d, $J = 10.2$ Hz), 3.23 (1H, tt, $J = 10.8$, 5.4 Hz), 2.97 (1H, d, $J = 10.2$ Hz), 2.41–2.36 (2H, m), 2.22 (1H, dt, $J = 14.4$, 3.6 Hz), 2.17 (1H, ddd, $J = 12.6$, 7.2, 3.6 Hz), 2.05 (1H, t, $J = 10.8$ Hz), 2.01–1.95 (1H, m), 1.89–1.84 (1H, m), 1.70–1.65 (1H, m), 1.66 (3H, s), 1.64–1.55 (1H, m), 1.39–1.30 (3H, m), 0.91 (3H, s), 0.88 (3H, s); ^{13}C NMR (150 MHz, C_6D_6) δ 168.8, 159.7, 140.2, 139.2, 128.51, 128.48, 127.64, 127.59, 127.5, 127.4, 105.1, 79.2, 77.7, 73.6, 72.6, 69.8, 53.9, 51.0, 38.4, 35.1, 34.8, 32.1, 31.5, 30.6, 28.0, 26.2, 21.1, 20.8, 14.8; LRMS *m/z*: 502 (M^+); HRMS calcd for $C_{33}H_{42}O_4$ (M^+) 502.3083, found: 502.3105.
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