Natural Product Synthesis

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Total Synthesis of Auripyrone A**

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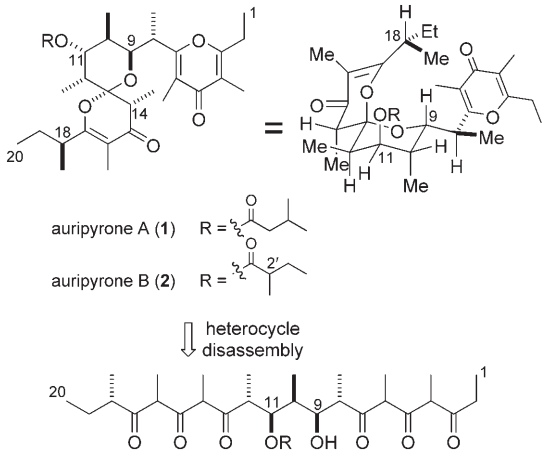
Dolabella auricularia, a sea hare from the *aplysiidae* family of marine opisthobranchs, has been a prolific source of bioactive metabolites, which range from peptides and depsipetides to polyketides, for over 40 years.[1] In 1996, the auripyrones A (**1**) and B (**2**) were added to this list when they were isolated



by Suenaga et al.[2] from the methanol extract of specimens of *D. auricularia* collected near Mie Prefecture, Japan. Structural elucidation revealed a characteristic polypropionate architecture, with a unique spiroacetal dihydropyrone core tethered to a γ-pyrone ring. Auripyrones A (**1**) and B (**2**) were shown to differ only in the nature of their respective C11 acyloxy side chains and exhibited moderate cytotoxicity against HeLa S_3 cells with IC_{50} values of 0.26 and 0.48 μg mL^{-1}, respectively. Suenaga et al.[2] assigned the complete relative stereochemistry of **1** using extensive ^{1}H NMR experiments, but they were unable to assign the configuration of the C2′ stereocenter of **2** or the absolute stereochemistry[3] of the natural products.

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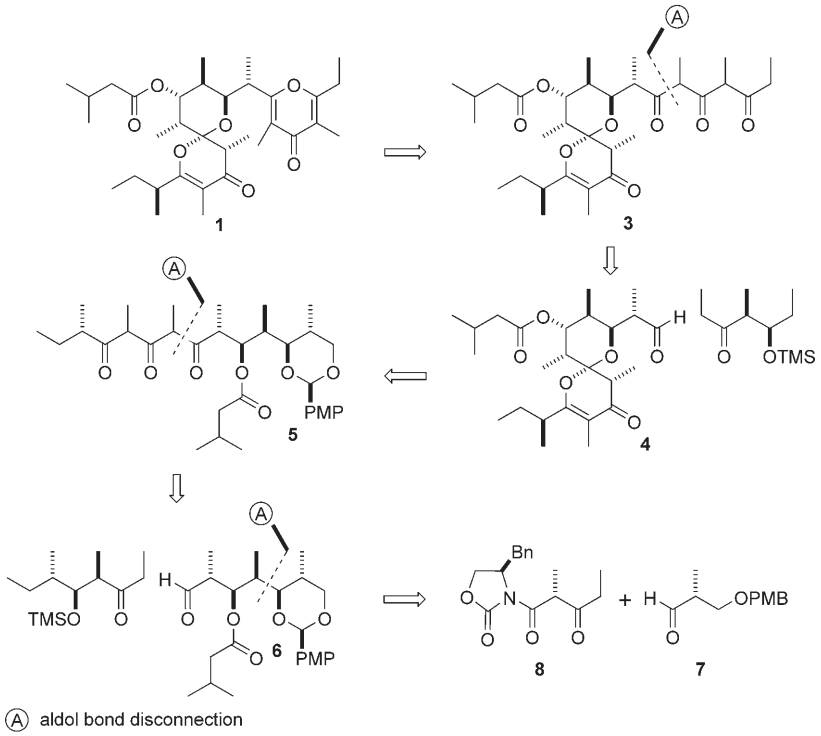
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

At the heart of the auripyrones, as evidenced by unraveling the heterocycles, is a *meso* stereopentad, flanked on both sides by two tricarbonyl systems. The C2 symmetry of this stereochemical array is broken only by the C19–C20 ethyl extension and the acyl group on the C11 oxygen atom. The presence of the C11 acyloxy moiety may constitute a biosynthetic protecting group, thus guiding the observed spiro cyclization in preference to competing cyclization events.

Herein, we describe the first total synthesis of auripyrone A (**1**) and identify the absolute stereochemistry of the natural product. We chose the reterosynthetic approach shown in Scheme 1.



Scheme 1. Retrosynthetic analysis of auripyrone A (**1**). Bn = benzyl, PMB = *para*-methoxybenzyl, PMP = *para*-methoxyphenyl, TMS = trimethylsilyl.

It was anticipated that a final-stage pyrone formation, which would give **1**, could be accomplished from triketone **3**, despite the potentially sensitive nature of the spiroacetal core. Formation of **3** was proposed from spiroacetal aldehyde **4** through a sequence of aldol addition, deprotection, and oxidation. One of the critical elements in the strategy was the formation of the correct stereoisomer of the spiroacetal dihydropyrone found in **4**, which was foreseen to arise from a thermodynamically controlled cyclization after removal of the acetal protecting group in **5**. Aldol addition, deprotection, and oxidation would provide tricarbonyl **5** from aldehyde **6**. To generate the correct stereopentad in **6**, we proposed the use of substrate control by employing the Evans dipropionate equivalent **8**,[4] in an aldol reaction with known[5] chiral aldehyde **7**, followed by *syn* reduction of the resultant β-hydroxy ketone.

Previous work[6] has shown that the formation of the sprioacetal dihydropyrone was unsuccessful without differentiation between the C9 and C11 hydroxy groups. We chose to use the acyloxy moiety found in **1** as the C11 protecting group, thus minimizing the reliance on formal protection sequences. Indeed, the final strategy does not require the introduction of any protecting groups within the linear sequence.

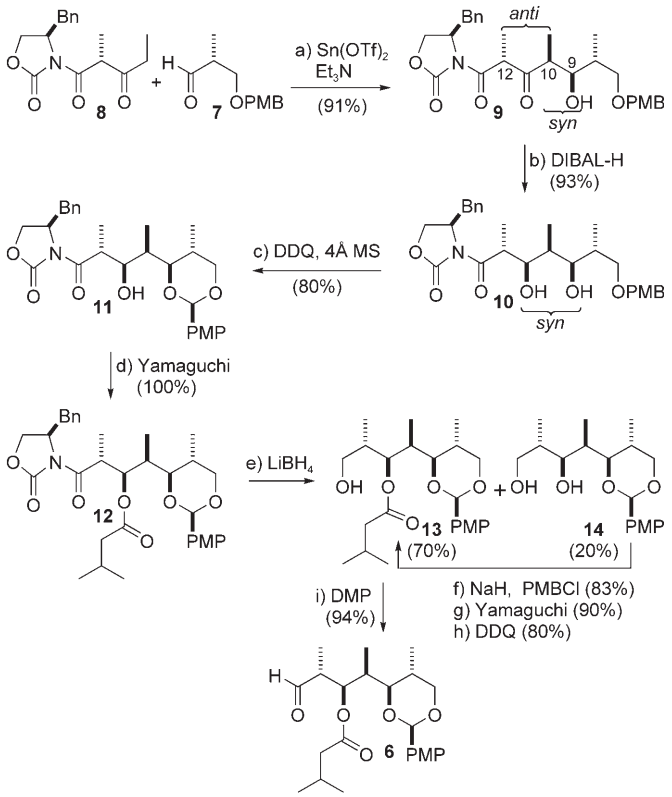
We began our synthesis from dipropionate equivalent **8** (available[4] from (*R*)-phenylalanine in five steps; Scheme 2). The Sn^{II} enolate of β-ketoimide **8**[7] underwent a highly selective double stereodifferentiating aldol addition with known[5] α-methyl aldehyde **7** to give the 9,10-*syn*,10,12-*anti* aldol product **9**. Subsequent reduction with DIBAL-H[7] of the adduct gave diol **10** as a single isomer, thus completing the construction of the stereopentad. The necessity for the reduction with DIBAL-H to be performed on the unprotected substrate is a small drawback to this highly efficient protocol.

Migration of the PMB group introduced with aldehyde **7** provided an efficient solution to the selective protection of diol **10**. In practice, treatment of **10** with DDQ under anhydrous conditions[8] afforded the crystalline *p*-methoxybenzilidene acetal **11** in good yield, thus selectively protecting the C9 hydroxy group. Treatment of **11** with isovaleric acid under conditions developed by Yamaguchi and co-workers[9] gave **12** in near quantitative yield. Thus, the required C11 acyloxy function for **1** was installed, thereby negating the use of a formal protecting group.

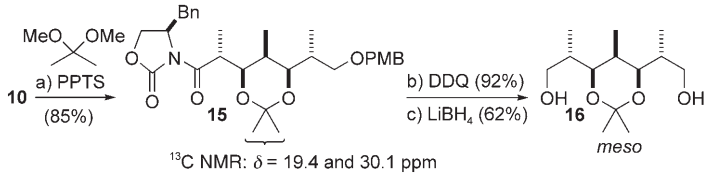
The treatment of **12** with $LiBH_4$[10] gave the desired primary alcohol **13** in good yield (70%), with only minor amounts of diol **14** (20%). The overall yield of **13** could be increased by processing the by-product **14** through the following sequence: 1) protection of the primary alcohol group with a PMB ether, 2) Yamaguchi esterification, and 3) DDQ-mediated cleavage of the PMB ether. Oxidation of **13** with DMP[11] gave aldehyde **6** in excellent yield.

The stereochemistry of the stereopentad in **10** was confirmed by using the simple strategy shown in Scheme 3. Treatment of the diol **10** with dimethoxypropane and catalytic PPTS gave the acetonide **15**, whose characteristic ^{13}C NMR shifts[12] of $\delta = 19.4$ and 30.1 ppm indicated a *syn*-diol relationship. Subsequent DDQ-mediated cleavage of the PMB ether and reductive removal of the auxiliary gave the *meso*-diol **16**, which displayed only nine ^{13}C NMR resonances and no optical rotation.

The preparation of the spiroacetal dihydropyrone **17** is shown in Scheme 4. Reaction of the Ti^{IV} enolate[7,13] of pentan-3-one (**18**) with (*S*)-2-methylbutanal (**19**; obtained from the oxidation of the commercially available (*S*)-2-methylbutanol) gave two separable aldol products **20** (15%) and **21** (65%). The major product was assigned as the *anti*-Felkin isomer **21** on the basis of a literature precedent.[14] Silyl protection of **21** with TMSOTf/lutidine completed this short

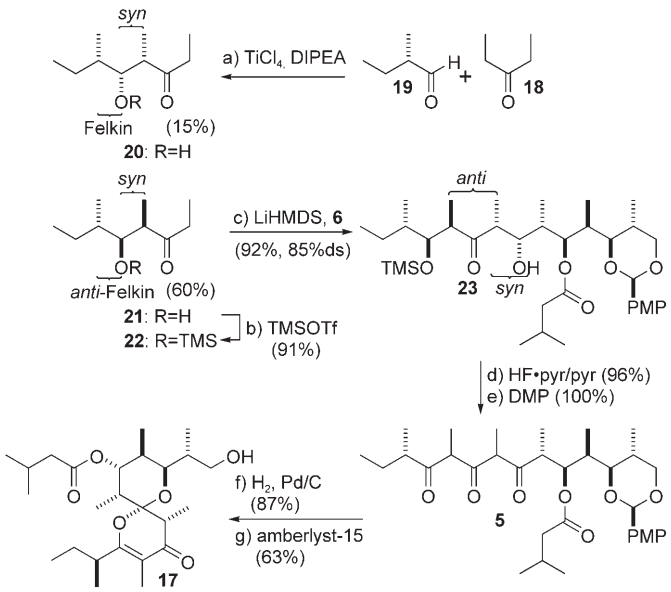


Scheme 2. Installation of the stereopentad, differential protection, and construction of the aldehyde **6**. Reagents and conditions: a) $Sn(OTf)_2$ (1.3 equiv), Et_3N (1.3 equiv), **7** (1.5 equiv), CH_2Cl_2, −78 °C, 30 min, 91 %; b) DIBAL-H (4.0 equiv), Et_2O, −78 °C, 1 h, 93 %; c) DDQ (1.2 equiv), 4-Å powdered molecular sieves, CH_2Cl_2, 0 °C, 5 h, 80 %; d) 2,4,6-trichlorobenzoyl chloride (8.5 equiv), 4-DMAP (19.0 equiv), Et_3N (9.0 equiv), isovaleric acid (5.0 equiv), toluene, −78 °C→RT, 1.5 h, 100 %; e) $LiBH_4$ (1.2 equiv), EtOH (1.2 equiv), Et_2O, −10 °C, 3.5 h, 63 %; f) NaH (3.0 equiv), PMBCl (1.2 equiv), THF, room temperature, 3 h, 83 %; g) 2,4,6-trichlorobenzoyl chloride (17.0 equiv), 4-DMAP (38.0 equiv), Et_3N (18.0 equiv), isovaleric acid (10.0 equiv), toluene, −78 °C→RT, 1.5 h, 90 %; h) DDQ (1.3 equiv), phosphate buffer (pH 7), CH_2Cl_2, 0 °C, 3 h, 80 %; i) DMP (1.5 equiv), CH_2Cl_2, room temperature, 1 h, 94 %. OTf = trifluoromethanesulfonate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoqinone, DIBAL-H = diisobutylaluminum hydride, 4-DMAP = 4-(dimethylamino)pyridine, DMP = Dess–Martin periodinane, $LiBH_4$ = lithium borohydride, PMBCl = *p*-methoxybenzyl chloride.



Scheme 3. Construction of the *meso*-diol **16** to confirm of the relative stereochemistry of the stereopentad. Reagents and conditions: a) $(MeO)_2C(CH_3)_2$, PPTS (cat.), CH_2Cl_2, room temperature, 3 h, 85 %; b) DDQ (1.5 equiv), phosphate buffer (pH 7), CH_2Cl_2, 0 °C, 3 h, 92 %; c) $LiBH_4$ (2.4 equiv), EtOH (2.4 equiv), Et_2O, −10 °C, 1.5 h, 62 %. PPTS = pyridinium *p*-toluenesulfonate.

synthesis of enantiomerically pure ketone **22** required for coupling with aldehyde **6**.



Scheme 4. Construction of the spiroacetal dihydropyrone **17**. Reagents and conditions: a) **18**, $TiCl_4$ (1.2 equiv), DIPEA (1.4 equiv), **19** (1.5 equiv), CH_2Cl_2, −78 °C, 1 h, 60 %; b) TMSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, −90 °C, 10 min, 91 %; c) LiHMDS (1.1 equiv), **6** (0.5 equiv), THF, −78 °C, 2 h, 92 %, 85 % *de*; d) HF·pyr/pyr, THF, room temperature, 45 min, 96 %; e) DMP (3.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, room temperature, 1 h, 100 %; f) H_2, Pd/C (70 % w/w), EtOH, room temperature, 30 min, 87 %; g) amberlyst-15 (50 % w/w), CH_2Cl_2, −50 °C→RT, 5 h, 63 %. DIPEA = *N*,*N*-diisopropylethylamine, LiHMDS = lithium hexamethyldisilazide, Pd/C = palladium on activated carbon 10 % w/w, pyr = pyridine.

Ketone **22** was treated with LiHMDS at −78 °C, and the addition of aldehyde **6** gave the major aldol product **23** (78 %) and other isomers (11 %) after quenching. The configuration of the newly generated stereocenters in the major product **23** were tentatively assigned on the assumption that the *syn*/*anti* preference of the ketone[15] dominates in this double stereodifferentiating aldol reaction. In any case, the configuration of these newly formed stereocenters was not critical as they were either lost upon oxidation or became epimerizable in subsequent steps. To that end, the TMS group was removed with buffered HF·pyridine, and double oxidation with DMP afforded triketone **5** as a mixture of the keto and enol forms.

After extensive experimentation, spiroacetal dihydropyrone **17** was found to be most readily available from hydrogenolysis (H_2, Pd/C) of acetal **5** followed by stirring of the purified reaction product with amberlyst-15 resin[16] in CH_2Cl_2 for several hours. Gratifyingly, the cascade cyclization proceeded under thermodynamic control, thus giving **17** in good yield (63 %) and with high diastereoselectivity (94 % *ds*).[17] Two-dimensional NOE interaction experiments allowed us to confirm the total relative stereochemistry and, importantly, establish the configuration of the dioxaspiro center unambiguously.[18] There was also a good correlation of the ^1H and ^{13}C NMR chemical shifts and coupling constants with those reported[2] for the sprioacetal dihydropyrone core of **1**.

The second aldol extension and final stages of the synthesis of **1** is shown in Scheme 5. Oxidation of alcohol **17** with DMP gave aldehyde **4** (91 %), ready for aldol extension.

The coupling of **4** with a single enantiomer of ketone (4*S*,5*R*)-**24** was anticipated to lower the number of isomeric products and thus simplify their isolation and characterization. The synthesis of **24** was readily achieved and began with *N*-acyloxazolidinone **25**[4] in a four-step sequence which consisted of *syn*-aldol addition, transamination,[19] addition of Grignard reagents, and finally silyl protection (66% over four steps). Enolization of **24** with LiHMDS followed by reaction with **4** gave the elaborate adduct **26** in excellent yield (94%) and as a separable mixture of two diastereomers (88% *ds*). The configuration of the major product **26** was again tentatively assigned on the assumption that the *syn*/*anti* preference of the ketone[15] dominated in this double stereodifferentiating aldol reaction. Pleasingly, the use of the mild enolization conditions and the enantiomerically pure ketone had again enabled isolation of the desired aldol product in high yield and with good stereoselectivity.

The silyl group was removed with HF·pyr/pyr and the resultant diol **27** was oxidized with DMP to give the precursor triketone **3** as a mixture of the keto and enol forms. With the key precursor in hand, we turned our attention to the final formation of the pyrone ring. The methods developed by Yamamura and co-workers (PPh_3/CCl_4 and dimethylsulfoxide (DMSO)/$(COCl)_2$)[20] for the conversion of 1,3,5-triketones into the corresponding γ-pyrones under mild conditions have proved successful when employed by Paterson[9,21] and Arimoto[22] on relatively simple systems. Unfortunately the application of either of these conditions to **3** led to mixtures of decomposition products, in which the spiroacetal dihydropyrone ring was absent, despite apparent formation of a pyrone ring in a number of cases.

Recent studies[23] in our group have shown that the pyrone ring system found in tridachiahydropyrone can be formed in good yield from the appropriate β,δ-diketoacids by treatment with P_2O_5 supported on celite. Application of these conditions to **3** proved successful, and the reaction was further optimized by the addition of amberlyst-15 resin, which is thought to aid the reaction by increasing the rate of the triketone tautomerization. In the optimized procedure, **3** was stirred with the amberlyst-15 resin for several minutes, before P_2O_5 supported on celite was added and the reaction mixture stirred overnight. After filtration and flash chromatography, **1** was isolated in 39% yield. Synthetic **1** exhibited identical spectral data (^1H and ^{13}C NMR, UV/Vis, IR, and MS), as well as melting point, to those reported by Suenaga et al.[2] Notably, the optical rotation of synthetic **1**, $[\alpha]_D^{20} = +33°$ ($c = 0.2$, $CHCl_3$), was the same sign as that reported $[\alpha]_D^{26} = +28°$ ($c = 0.083$, $CHCl_3$),[2] thus establishing the absolute configuration of the natural product **1** (see Table 1).

The chemistry described herein constitutes an efficient, asymmetric synthesis of the cytotoxic marine polypropionate auripyrone A (**1**) in 16 steps and 6.2% yield from ketone **8** and aldehyde **7**, and thus establishes the absolute stereochemistry of the natural product. Our strategy employs substrate control to develop the stereopentad unit and introduces a novel method for the installation of γ-pyrone rings from 1,3,5-triketones.

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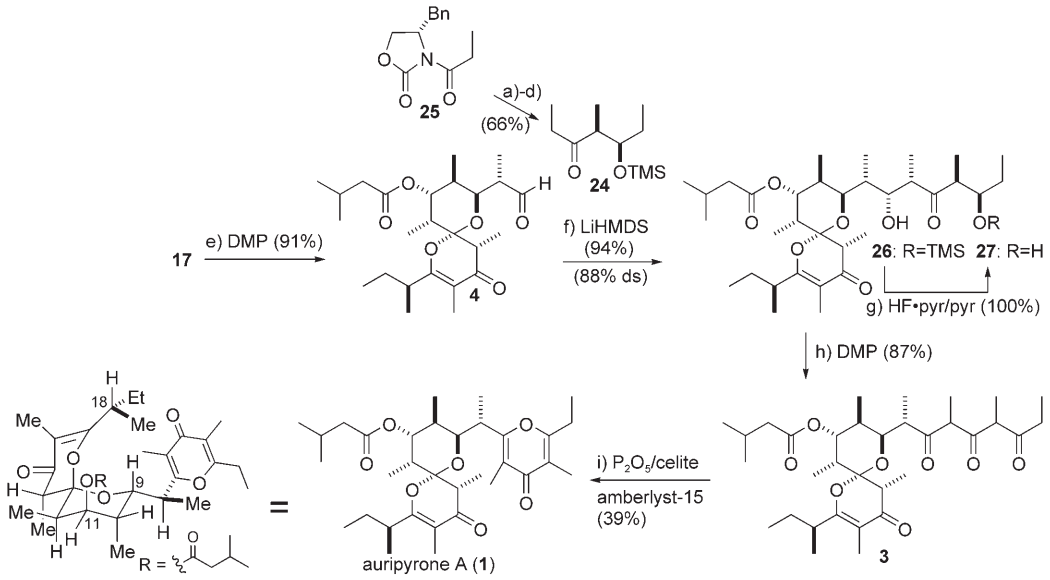

Scheme 5. Construction of the γ-pyrone ring and completion of the synthesis of **1**. Reagents and conditions: a) Bu_2BOTf (1.2 equiv), Et_3N (1.3 equiv), propanal (2.0 equiv), CH_2Cl_2, −78→0°C, 1.5 h, 88%; b) MeONH(Me)·HCl (2.0 equiv), $AlMe_3$ (2.0 equiv), CH_2Cl_2, room temperature, overnight, 100%; c) EtMgBr (3.0 equiv), Et_2O, room temperature, overnight, 88%; d) TMSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, −90°C, 30 min, 85%; e) DMP (1.5 equiv), CH_2Cl_2, room temperature, 1 h, 91%; f) LiHMDS (1.0 equiv), **4** (0.13 equiv), THF, −78°C, 1 h, 94%, 88% *de*; g) HF·pyr/pyr, THF, room temperature, 45 min, 100%; h) DMP (4.0 equiv), CH_2Cl_2, room temperature, 1 h, 87%; i) amberlyst-15 (50% w/w), P_2O_5 (4.0 equiv), celite, CH_2Cl_2, room temperature, overnight, 39% (based on 40% recovery of starting material).

Table 1: Selected physical properties for **17, 27**, and **1**.

17: $R_f = 0.25$ (silica gel, Et_2O/CH_2Cl_2 15:85); $[\alpha]_D^{20} = +107.5°$ ($c = 0.4$, CH_2Cl_2); IR (film): $\tilde{\nu} = 3478, 1732, 1669, 1624, 1462, 1387, 1371, 1294, 1166, 1095, 1058, 1038, 1010, 986, 918\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 4.93$ (t, $J = 3.6$ Hz, 1H), 3.83 (dd, $J = 10.2$, 2.4 Hz, 1H), 3.49 (dd, 10.8, $J = 5.4$ Hz, 1H), 3.37–3.34 (m, 1H), 2.50–2.44 (m, 1H), 2.43 (q, $J = 6.6$ Hz, 1H), 2.20–2.13 (m, 3H), 1.89 (s, 3H), 1.87 (qd, $J = 7.2$, 4.2 Hz, 1H), 1.81–1.73 (m, 2H), 1.61–1.55 (m, 1H), 1.54–1.40 (m, 2H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.06 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.0$ Hz, 3H), 0.88 (t, $J = 7.8$ Hz, 3H), 0.88 (d, $J = 6.0$ Hz, 3H), 0.80 (d, $J = 7.2$ Hz, 3H), 0.67 (d, $J = 7.2$ Hz, 3H), 0.56 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.5 MHz, C_6D_6): $\delta = 192.8, 172.0, 167.3, 108.0, 105.3, 75.1, 71.8, 66.6, 44.6, 44.0, 37.7, 36.6, 34.2, 31.9, 27.4, 26.3, 22.4, 22.3, 16.6, 12.6, 12.4, 12.0, 10.0, 9.4, 8.0$ ppm; HR ESI MS: calcd for $C_{25}H_{42}O_6Na^+$ [$M + Na^+$]: 461.2874; found: 461.2879; EI MS m/z (%): 197 (15), 149 (22), 111 (17), 97 (30), 85 (55), 83 (67), 72 (51), 70 (59), 57 (100), 55 (71).

27: $R_f = 0.26$ (silica gel, Et_2O/CH_2Cl_2 20:80); $[\alpha]_D^{20} = +76.9°$ ($c = 0.4$, CH_2Cl_2); IR (film): $\tilde{\nu} = 3505, 1734, 1670, 1620, 1459, 1388, 1373, 1346, 1294, 1254, 1212, 1166, 1120, 1094, 1058, 1009, 986, 964, 918\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 4.96$ (t, $J = 3.6$ Hz, 1H), 4.15 (br s, 1H), 3.98 (dd, $J = 10.2$, 1.8 Hz, 1H), 3.77 (br m, 1H), 2.81 (br s, 1H), 2.63 (qd, $J = 7.2$, 4.2 Hz, 1H), 2.53–2.43 (m, 3H), 2.39 (q, $J = 6.6$ Hz, 1H), 2.24–2.16 (m, 3H), 1.95–1.84 (m, 3H), 1.84 (s, 3H), 1.61–1.55 (m, 1H), 1.55–1.50 (m, 1H), 1.49–1.43 (m, 1H), 1.37–1.31 (m, 1H), 1.14 (d, $J = 7.2$ Hz, 3H), 1.08 (d, $J = 6.6$ Hz, 3H), 1.07 (d, $J = 6.6$ Hz, 3H), 1.03 (d, $J = 7.2$ Hz, 3H), 0.99 (t, $J = 7.2$ Hz, 3H), 0.94 (t, $J = 7.2$ Hz, 3H), 0.92 (d, $J = 6.0$ Hz, 3H), 0.91 (d, $J = 6.0$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H), 0.76 (d, $J = 6.6$ Hz, 3H), 0.76 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 220.2, 194.0, 172.1, 168.4, 107.5, 105.5, 75.2, 73.8, 70.3, 68.8, 50.5, 49.6, 44.5, 44.0, 38.2, 37.9, 34.1, 32.0, 27.6, 27.1, 26.3, 22.5, 22.4, 16.6, 12.4, 12.0, 11.0, 10.9, 10.7, 9.9, 9.8, 9.3, 7.9$ ppm; HR ESI MS: calcd for $C_{33}H_{56}O_8Na^+$ [$M + Na^+$]: 603.3867; found: 603.3863; EI MS m/z (%): 197 (52), 168 (9), 139 (14), 109 (15), 85 (24), 57 (100).

1: m.p.: 171–173 °C (172–176 °C)[2]; $R_f = 0.27$ (silica gel, Et_2O/CH_2Cl_2 50:50); $[\alpha]_D^{20} = +33.3°$ ($c = 0.2$, $CHCl_3$); IR (film): $\tilde{\nu} = 1729, 1656, 1626, 1618, 1459, 1419, 1386, 1374, 1291, 1251, 1166, 1091, 1058, 1010, 984, 963, 919\ cm^{-1}$; UV/Vis (MeOH) λ_{max} (ε): 260 (18200), 220 nm (10100 $M^{-1}cm^{-1}$); ^1H NMR (600 MHz, C_6D_6): $\delta = 4.92$ (t, $J = 3.3$ Hz, 1H), 3.98 (dd, $J = 10.2$, 2.1 Hz), 2.76 (dq, $J = 10.2$, 7.2 Hz, 1H), 2.32 (q, $J = 6.6$ Hz, 1H), 2.31 (dq, $J = 15.0$, 7.5 Hz, 1H), 2.26 (dqd, $J = 7.2$, 7.2, 3.6 Hz, 1H), 2.21–2.16 (m, 1H), 2.18–2.11 (m, 2H), 2.10 (dq, $J = 15.0$, 7.5 Hz, 1H), 2.03 (s, 3H), 1.98 (s, 3H), 1.85 (qd, $J = 7.2$, 3.6 Hz, 1H), 1.83–1.80 (m, 1H), 1.64 (s, 3H), 1.56–1.48 (m, 1H), 1.41–1.34 (m, 1H), 1.12 (d, $J = 6.6$ Hz, 3H), 0.99 (d, $J = 7.2$ Hz, 3H), 0.91 (d, $J = 6.0$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.90 (t, $J = 7.5$ Hz, 3H), 0.84 (t, $J = 7.5$ Hz, 3H), 0.78 (d, $J = 7.2$ Hz, 3H), 0.74 (d, $J = 7.2$ Hz, 3H), 0.65 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 191.8, 178.5, 172.0, 166.2, 162.1, 161.6, 121.3, 118.1, 107.8, 105.0, 75.2, 70.6, 44.5, 44.0, 37.2, 36.7, 34.1, 31.7, 26.4, 26.3, 24.7, 22.5, 22.3, 16.0, 12.1, 12.0, 11.9, 11.0, 10.7, 9.7, 9.5, 8.9, 8.1$ ppm; HR ESI MS: calcd for $C_{33}H_{50}O_7Na^+$ [$M + Na^+$]: 581.3449; found: 581.3448; EI MS m/z (%): 558 (M^+, 43), 501 (9), 457 (11), 391 (6), 317 (20), 261 (12), 221 (31), 193 (100), 180 (43), 151 (11), 137 (18), 85 (17), 83 (22), 57 (68), 55 (15).

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[3] The structure drawn by Suenaga et al.[2] in the report on the isolation of the natural product was an arbitrary choice for the absolute stereochemistry of the auripyrones. We chose to target the enantiomer of that depicted by Suenaga et al. because of the commercial availability of only the *S* enantiomer of 2-methylbutanol, which we used to gain access to the remote C18 stereocenter.

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