Total Synthesis of Rhizoxin D

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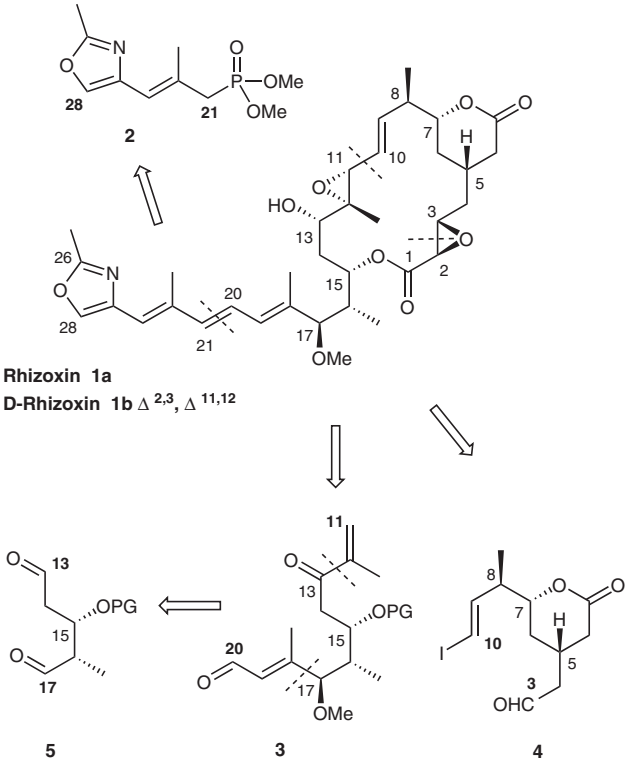
Abstract: A total synthesis of rhizoxin D (**1b**), a 16-membered antitumoral macrolide, is reported. The strategy relies on the application of a Brown allylation reaction for the C15 and C16 asymmetric centres control. Installation of the C17 hydroxyl function with concomitant building of the (*E*)-C18-C19 double bond was effected by a diastereoselective addition of vinyllithium derivative **15** to aldehyde **10**. The terminal enone group was then introduced to achieve the preparation of C11-C20 segment **23**. A Heck coupling reaction between C11-C20 fragment **23** and C3-C10 segment **24** (previously prepared in our laboratory) was performed with success to deliver the C3-C20 fragment **25**. The total synthesis of rhizoxin D (**1b**) was achieved after transformation of **25** into the macrolactone **28**, and coupling the C21-C28 side chain using a Wittig–Wadsworth–Emmons reaction.

Key words: rhizoxin D, total synthesis, Heck cross-coupling, vinyllithium reagents, macrolactonisation

In our search for new antitumor agents, the unique structure of rhizoxin (**1a**) and its remarkable biological activities led us to undertake the total synthesis of this compound.[1,2] Rhizoxin (**1a**), a 16-membered macrolide, was isolated in 1984 from *Rhizopus chinensis* Rh-2[3] as the pathogen of rice seedling blight. It exhibits potent in vitro cytotoxicity[4] and in vivo antitumor activities (Scheme 1).[5] Treatment of ovarian cancer, colorectal and renal cancer, breast cancer and melanoma are currently under investigations in phase II clinical trials.[6] Bisdesepoxide rhizoxin (or rhizoxin D, **1b**), isolated from the same organisms[7] in 1986, shows similar antitumor properties and could be considered as an intermediate in the synthesis of rhizoxin (**1a**).

Our retrosynthetic analysis of rhizoxin D (**1b**), outlined in Scheme 1, involves the preparation of the three C21-C28 **2**, C11-C20 **3** and C3-C10 **4** sub-units. The key disconnection at C10-C11 is based on a sp^2-sp^2 type Pd(0)-mediated cross-coupling reaction between C3-C10 vinyl iodide **4** and C11-C20 enone **3**. Formation of the macrolactone core was envisaged via an intramolecular Wittig reaction, and the side chain C21-C28 would be coupled using phosphonate **2** in an olefination reaction.

In a precedent work, we described the synthesis of C3-C10 iodo-aldehyde **4**,[8] and here we wish to report the enantioselective preparation of the C11-C20 segment **3**



Scheme 1

and the establishment of the C10-C11, C15-C3 and C20-C21 linkages.

The synthesis of sub-unit **3**, quite original, is based on the extension at both sides of the key central dialdehyde C13-C17 (**5**).

Preparation of the optically active aldehyde **10** was easily accomplished (Scheme 2). Monoprotected propanediol **6** was first oxidized into aldehyde **7** in 77% yield, which was then submitted to a Brown aldehyde allylation. The diastereomerically pure homoallylic alcohol **8** was thus obtained in 80% yield (ee >95%).[9] After protection of the secondary alcohol at C15, the resulting silyl ether **9** (90% yield) was ozonised to furnish aldehyde **10** in 95% yield (Scheme 2).[10]

The required homologation to construct the C13-C20 fragment involved an addition of lithium derivative **15** to aldehyde **10**. We took advantage of a stannylcupration reaction we developed earlier to prepare (*E*)-iodovinyl compound **14** in a diastereoselective fashion.[11]

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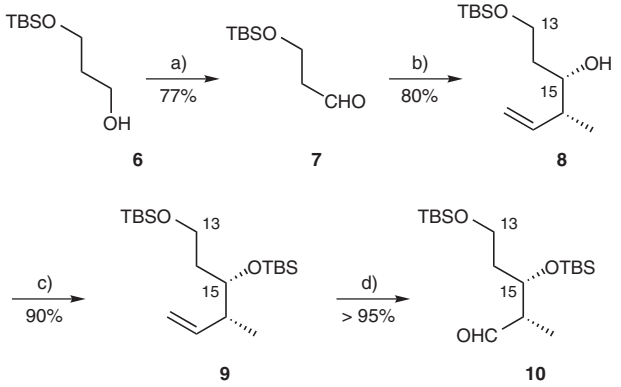
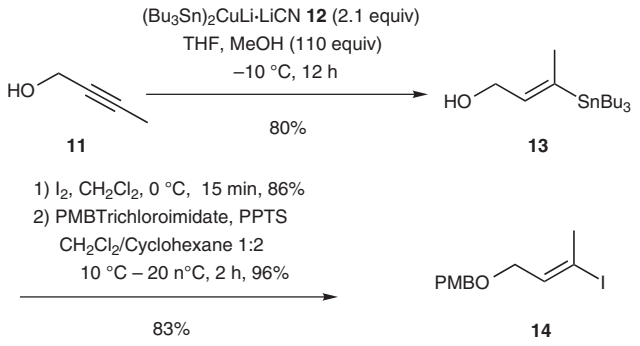


Scheme 2 a) SO_3·pyridine, Et_3N, DMSO, 20 °C, 10 min; b) i) *tert*-BuOK, *trans*-but-2-ene, *n*-BuLi, THF, –78 °C, 5 min, and –45 °C, 20 min; ii) (+)-$Ipc_2B(OMe)$, Et_2O, –78 °C, 15 min, and –78 °C, 40 min; iii) BF_3·OEt_2, –78 °C; iv) **7**, THF, –78 °C, 4 h; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 20 °C, 1.5 h; d) i) O_3, CH_2Cl_2–MeOH 1:1, pyridine (6 equiv), –78 °C; ii) Me_2S, –78 °C to 20 °C, 12 h.



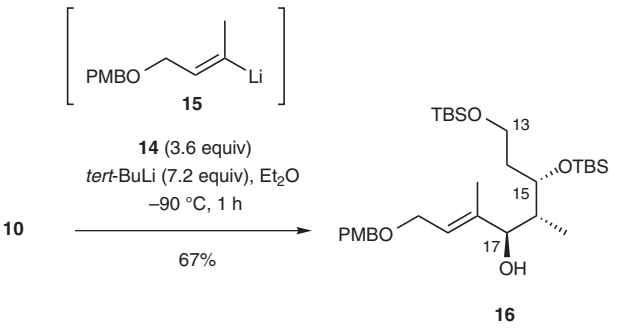
Scheme 3

Treatment of butynol **11** with dilithium *bis*-tributylstannyl(cyano)cuprate (**12**) in THF and MeOH (110 equiv) at –10 °C for 12 hours resulted in the formation of the expected pure (*E*)-vinyltin derivative **13** in 80% isolated yield (Scheme 3). A subsequent Sn/I exchange followed by a protection of the primary alcohol led to **14** in 66% overall yield.

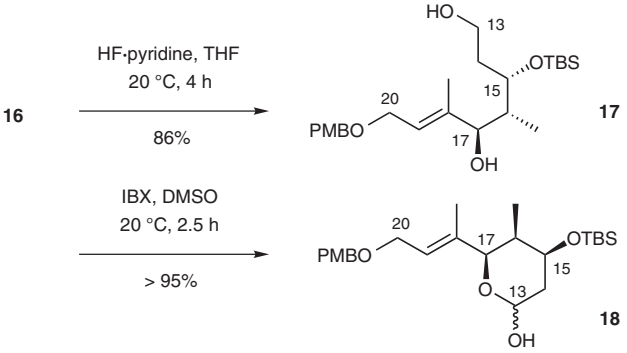
Lithium derivative **15**, prepared from **14** by a halogen–metal exchange using *tert*-butyllithium in diethyl ether at –90 °C, reacted with aldehyde **10** to conduct to the suitable adduct **16** in 67% isolated yield (dr 75:25, Scheme 4).[12]

Confirmation of the structure of diastereomer **16** was obtained by ^1H NMR analysis of lactol **18** (Scheme 5). The latter was prepared from **16** in two steps, selective deprotection of the primary alcohol (**17**, 86% yield) and IBX oxidation (**18**, 95% yield).

Conversion of **16** to enone **3** was then required as well as methylation of the C17 hydroxyl group. Unfortunately, classical conditions (NaH, MeI) applied to this transformation resulted in a partial rearrangement of the C15 silyl ether to the C17 position. To circumvent this difficulty, a MeOTf methylation in presence of 2,6-di-*tert*-Bu-4-



Scheme 4

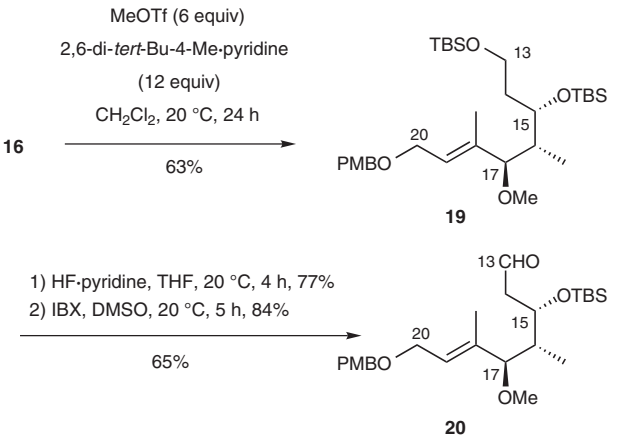


Scheme 5

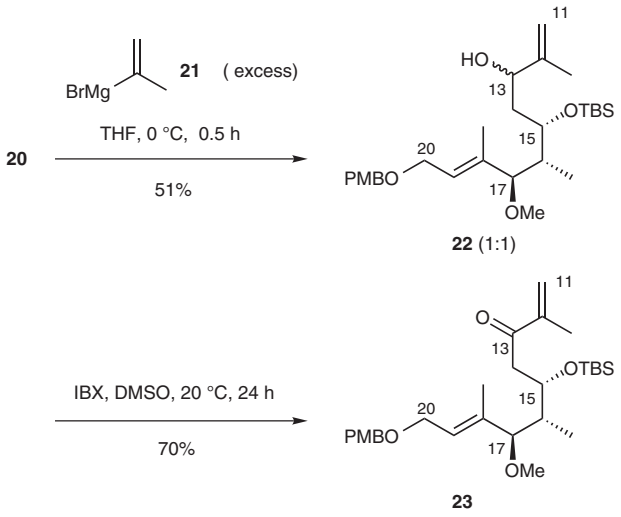
methyl pyridine was performed;[13] these conditions allowed the preparation of **19** in 63% yield (Scheme 6).

Transformation of **19** to aldehyde **20** was then easily carried out after regeneration of the primary alcohol (HF·pyridine, 77% yield) and subsequent IBX oxidation (84% yield).

First attempts to form derivative **22** utilising 2-lithio-2-propene were low yielding and not easily reproducible.[14] However, with Grignard reagent **21**,[15] allylic alcohol **22** was obtained in 51% yield (Scheme 7). An IBX oxidation of **22** then delivered the expected enone **23** in 70% yield.



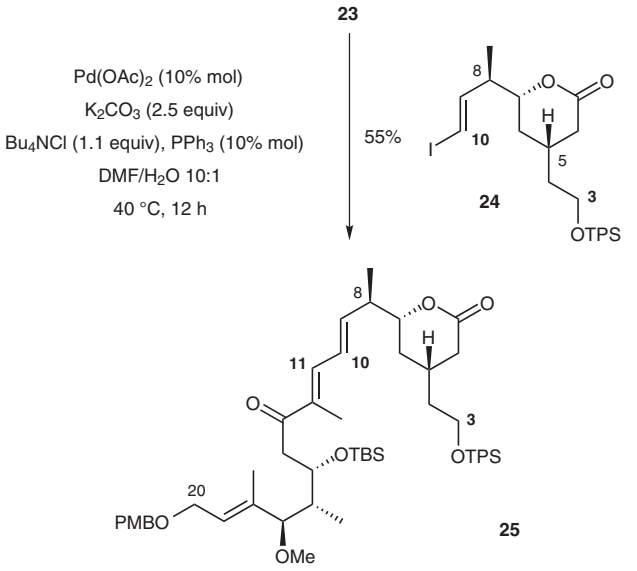
Scheme 6



Scheme 7

Having secured the synthesis of C11-C20 fragment **3**, we then desired to validate our synthetic approach, so we investigated the coupling reaction between the C11-C20 and C3-C10 fragments **23** and **24** (Scheme 8).

Under Heck–Jeffery conditions[16] [$Pd(OAc)_2$, K_2CO_3, Bu_4NCl, PPh_3, DMF–H_2O], reaction of **23** with **24** led to the expected C3-C20 fragment **25** of rhizoxin D (**1b**) in 55% yield.[17]



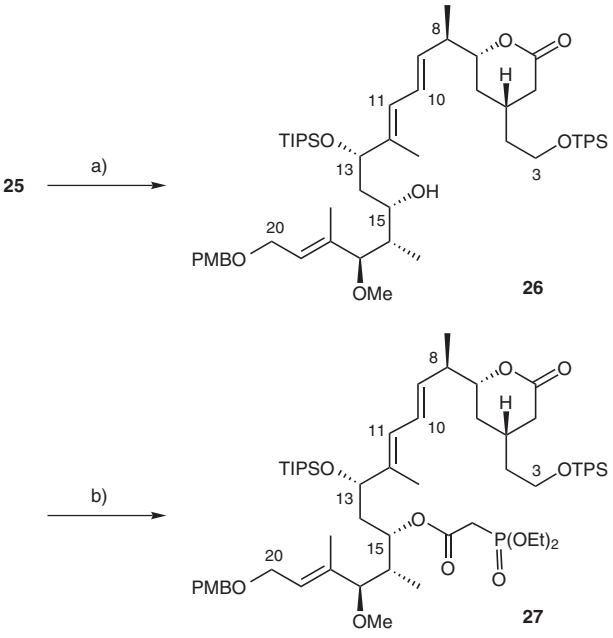
Scheme 8

The precursor of the intramolecular Wittig–Wadsworth–Emmons reaction was then synthesised from **25**. The TBS ether of **25** was hydrolysed (Amberlyst 15/MeOH, 85%) before stereoselective reduction of the C13 ketone [$Me_4NBH(OAc)_3$, 90%, de >98%].[18] Selective protection of the C13 hydroxyl function (TIPSOTf, 2,6-lutidine, CH_2Cl_2) into the TIPS ether **26** (85% yield), then gave the opportunity to install the phosphonoacetate at C15. Treatment of **26** with diethylphosphonoacetic acid, DCC and DMAP cleanly delivered the expected ester **27** in 80% yield (Scheme 9).

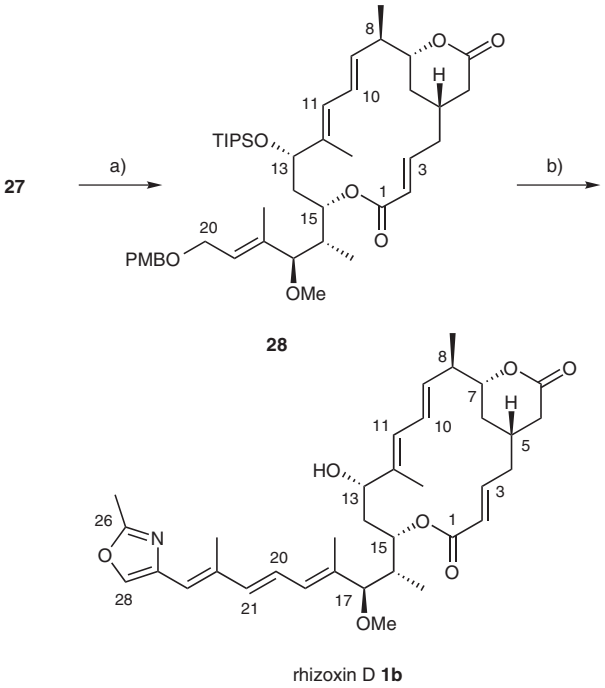
Selective removal of the primary alcohol at C3 could be effected using the White method treating with TASF, DMF, 20 °C, 12 hours protocol (60% yield); preparation of the aldehyde at this position was then carried out by oxidation with IBX (95% yield). The final intramolecular macrocyclisation was then realised under Masamune–Roush conditions [$(i\text{-Pr})_2$NEt, LiCl], to deliver the macrolactone core of rhizoxin D (**28**) in 50% yield (Scheme 10).

After displacement of the PMB protecting group at C20 (DDQ, CH_2Cl_2, H_2O, 20 °C, 2 h, 75% yield), IBX oxidation (90% yield) delivered the required aldehyde, which was directly engaged in a Horner–Wadsworth–Emmons reaction with methyl phosphonate **2** (*t*-BuOK, DME, 0 °C, 30% yield). In the last step of the sequence, the triisopropylsilyl group at C13 was readily removed by treatment with HF·pyridine–THF to furnish rhizoxin D (**1b**) in 55% yield.

In conclusion, a new and convergent preparation of rhizoxin D (**1b**) is described. The synthesis features the formation of the pivotal segment C11-C20 **3** and an original Heck coupling reaction at C10-C11 between the Northern and Southern sub-units.



Scheme 9 a) i) Amberlyst 15, MeOH, 20 °C 2 h, 85%; ii) $Me_4NBH(OAc)_3$ (1.3 equiv), HOAc, MeCN, –50 °C to 20 °C, 12 h, 90%; iii) TIPSOTf (1.1 equiv), 2,6-lutidine, CH_2Cl_2, –10 °C, 85%; b) diethylphosphonoacetic acid, DCC, DMAP, 20 °C, 3 h, **80**%.



Scheme 10 a) i) TASF, DMF, 0 °C, 12 h, 60%; ii) IBX, DMSO, 20 °C, 1 h, 95%; iii) $(i\text{-Pr})_2$NEt, LiCl, MeCN, 12 h, 50%; b) i) DDQ, CH_2Cl_2, H_2O, 20 °C, 2 h, 75%; ii) IBX, DMSO, 20 °C, 1 h, 90%; iii) **2**, *t*-BuOK, DME, 0 °C, 30%; iv) HF·pyridine, THF 20 °C, 48 h, 55%.

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(17) Some selected data:
Compound **16**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = –0.06 (s, 3 H), –0.05 (s, 3 H), 0.00 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 0.91 (s, 9 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 1.57 (s, 3 H), 1.63–1.80 (m, 1 H,), 1.89 (q, *J* = 6.3 Hz, 2 H), 3.45 (s, 1 H, OH), 3.55 (dt, *J* = 11.9, 6.3 Hz, 2 H), 3.80 (s, 3 H), 3.90–3.99 (td, *J* = 6.3, 3.0 Hz, 1 H), 4.09 (d, *J* = 6.6 Hz, 2 H), 4.37 (br s, 1 H), 4.45 (s, 2 H), 5.79 (t, *J* = 6.6 Hz, 1 H), 6.88 (m, 2 H), 7.23 (m, 2 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = –4.76 (2 CH_3), –4.45 (2 CH_3), 10.8 (CH_3), 14.0 (CH_3), 17.9 (C), 18.2 (C), 25.9 (6 CH_3), 37.4 (CH), 37.6 (CH_2), 55.2 (CH_3), 59.7 (CH_3), 66.0 (CH_2), 71.4 (CH_2), 74.0 (CH), 74.6 (CH), 113.7 (2 CH), 121.2 (CH), 129.3 (2 CH), 130.7 (C), 139.3 (C), 159.0 (C). IR (film): 3448, 2955, 2857, 1650, 1510, 1380, 1250 cm^{-1}. MS (CI, NH_3): *m*/*z* = 553 [MH^+]. Anal. Calcd for $C_{30}H_{56}O_5Si_2$ (552.93): C, 65.17; H, 10.21. Found: C, 65.20; H, 10.23. $[\alpha]_D$ +4.4 (*c* 1.92, $CHCl_3$).
Compound **23**: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.13 (s, 3 H), 0.78 (s, 9 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 1.58 (s, 3 H), 1.81 (s, 3 H), 1.83–1.93 (m, 1 H), 2.34 (dd, *J* = 15.2, 2.3 Hz, 1 H), 2.97 (dd, *J* = 15.2, 9.2 Hz, 1 H), 3.14 (s, 3 H), 3.16 (d, *J* = 7.3 Hz, 1 H), 3.78 (s, 3 H), 4.04–4.16 (m, 3 H), 4.42 (s, 2 H), 5.50 (t, *J* = 6.1 Hz, 1 H), 5.73 (s, 1 H), 5.93 (s, 1 H), 6.85 (m, 2 H), 7.25 (m, 2 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = –4.9 (CH_3), –4.8 (CH_3), 9.5 (CH_3), 11.9 (CH_3), 17.6 (CH_3), 17.9 (C), 25.7 (3 CH_3), 39.4 (CH_2), 42.1 (CH), 55.3 (CH_3), 56.1 (CH_3), 65.9 (CH_3), 70.1 (CH), 71.7 (CH_2), 88.7 (CH), 113.7 (2 CH), 125.3 (CH_2), 126.5 (CH), 129.4 (2 CH), 130.4 (C), 136.1 (C), 145.2 (C), 159.1, (C), 200.7 (C). IR (film): 2955, 2856, 2380, 1678, 1530, 1385, 1250 cm^{-1}. MS(CI, NH_3): *m*/*z* = 491 [MH^+]. Anal. Calcd for $C_{28}H_{46}O_5Si$ (490.75): C, 68.53; H, 9.45. Found: C, 68.69; H, 9.38. $[\alpha]_D$ –23.0 (*c* 1.23, $CHCl_3$).
Compound **25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 and 0.12 (2 s, 6 H), 0.79 (s, 9 H), 1.03–1.12 (m, 13 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 1.55 (m, 1 H), 1.57 (m, 2 H), 1.60 (s, 3 H), 1.82 (s, 3 H), 1.86 (m, 1 H), 1.91–2.12 (m, 2 H), 2.27 (dd, *J* = 15.3, 2.1 Hz, 1 H), 2.59–2.69 (m, 2 H), 3.18 (s, 3 H), 3.20 (d, *J* = 8.2 Hz, 1 H), 3.60 (dd, *J* = 15.3, 9.7, 1 H), 3.70 (t, *J* = 5.7 Hz, 2 H), 3.80 (s, 3 H), 4.05–4.19 (m, 4 H), 4.50 (2 d, *J* = 11.5 Hz, 2 H), 5.53 (t, *J* = 5.8 Hz, 1 H), 6.04 (dd, *J* = 14.6, 7.8 Hz, 1 H), 6.47 (dd, *J* = 14.6, 10.9 Hz, 1 H), 6.87 (m, 2 H), 7.00 (d, *J* = 10.9 Hz, 1 H), 7.10 (m, 2 H), 7.40 and 7.60 (2 m, 5 H). MS (CI, NH_3): *m*/*z* = 925 [MH^+].
Compound **28**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (dt, *J* = 12.5, 13.0 Hz, 1 H), 0.99 (d, *J* = 6.8 Hz, 3 H, H3), 1.07 (m, 21 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.60 (s, 3 H), 1.68 (m, 1 H), 1.72 (m, 1 H), 1.80 (m, 1 H), 1.80 (s, 3 H), 1.95 (ddd, *J* = 12.5, 11.5, 9.5 Hz, 1 H), 2.12 (dd, *J* = 17.5, 10.5 Hz, 1 H), 2.18 (m, 1 H), 2.30 (m, 1 H), 2.33 (dquint, *J* = 9.5, 7.0 Hz, 1 H), 2.52 (m, 1 H), 2.80 (dd, *J* = 17.5, 5.5 Hz, 1 H), 3.20 (s, 3 H), 3.31 (d, *J* = 9.0 Hz, 1 H), 3.68 (ddd, *J* = 11.5, 7.0, 3.0 Hz, 1 H), 3.80 (s, 3 H), 3.86 (dd, *J* = 11.5, 4.0 Hz, 1 H), 4.05 (d, *J* = 6.0 Hz, 2 H), 4.48 (d, *J* = 11.5 Hz, 1 H), 4.50 (d, *J* = 11.5 Hz, 1 H), 4.60 (dd, *J* = 10.5, 3.0 Hz, 1 H), 5.16 (dd, *J* = 15.0, 9.5 Hz, 1 H), 5.53 (t, *J* = 6.0 Hz, 1 H), 5.62 (dt, *J* = 14.5, 1.5 Hz, 1 H), 5.75 (d, *J* = 11.5 Hz, 1 H), 6.25 (dd, *J* = 15.0, 11.5 Hz, 1 H), 6.77 (ddd, *J* = 14.5, 10.5, 5.5 Hz, 1 H), 6.83 (m, 2 H), 7.08 (m, 2 H). IR (film): 2950, 2850, 1730, 1650, 1510, 1380, 1250, 1185 cm^{-1}. $[\alpha]_D$ –2 (*c* 0.12, $CHCl_3$).

(18) Spectral data are in excellent agreement with those previously reported. See ref. 7.