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Asymmetric synthesis of (+)-chloriolide

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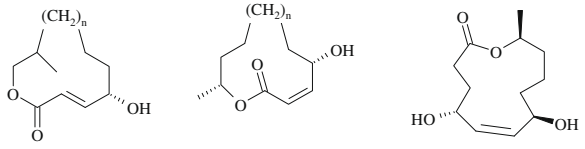
ABSTRACT

An asymmetric synthesis of 12-membered ring macrolide, chloriolide has been accomplished by adopting a linear strategy. Lipase-catalyzed enzymatic kinetic resolution (EKR), asymmetric alkynylation using Trost pro-phenol catalyst followed by Yamaguchi macrolactonization has been successfully employed to achieve the target molecule.

Chloriolide is a 12-membered ring macrolide which was obtained from solid substrate fermentation cultures of *Chloridium virescens var. chlamydosporum* (NRRL 37636) that was originally isolated from decayed wood by Jiao et al.[1] Chloriolide belongs to family of polyketide-derived fungal macrolactones (Scheme 1). Although the related cladospolides and patulolides have been reported to show antifungal and antibacterial activities, chloriolide was inactive against *Aspergillus flavus* and *Fusarium verticillioides*. Chloriolide was also inactive in antibacterial disk assays against *Staphylococcus aureus*, *Bacillus subtilis*. The antifungal activity of the original extract was attributed to the presence of the well-known antifungal metabolite monorden. Monorden (also known as radicicol) is produced by *Monicillium nordinii*, a mycoparasite isolated from fungi that attack forest trees, as well as a variety of other fungi.[2]

Total synthesis of structurally related patulolide has been reported in the literature.[3] In this Letter we would like to present asymmetric synthesis of (+)-chloriolide. During the course of our study the first asymmetric synthesis of the parent molecule has been reported by Haug and Kirsch[4] The retrosynthetic analysis is shown in Scheme 2. The main highlights of our synthetic strategy are Yamaguchi macrolactonization of properly functionalized *seco* acid in the penultimate step. The *seco* acid in turn can be easily constructed from two iterative three carbon homologation (alkynylation reaction with properly protected propargyl alcohol) reaction with hydroxyl protected aldehyde. The required hydroxyl protected aldehyde is thought to be constructed by an enzymatic kinetic resolution (EKR) strategy (Scheme 2).

The synthesis starts from 1,3-butane diol (**1**). Selective mono protection with TBSCl (*tert*-butyldimethylsilyl chloride) by McDougals protocol,[5] yielded the mono TBS protected ether **2** in 90% yield. With this racemic mono protected ether, enzymatic kinetic resolution (EKR) was achieved using vinyl acetate, CAL-B (*Candida antartica* lipase) and DIPE (diisopropyl ether) as solvents to afford the corresponding (*R*)-acetate **3** (yield = 48%, ee = 99%) and (*S*)-alcohol **4** (yield = 48%, ee = 97%) according to Kazlauskas empirical rule.[6] The (*S*)-alcohol **4** was required for our synthetic exercise, hence the ent-**3** obtained from methanolic hydrolysis of (*R*)-**3** was inverted by Mitsunobu inversion followed by acetate group deprotection afforded the required (*S*)-**4** in good yield (93% in two steps). The alcohol functionality in (*S*)-**4** was protected as its PMB (*para*-methoxybenzyl) ether by treating with PMB-imidate[7] in the presence of a catalytic amount of CSA (camphorsulfonic acid) to yield compound **5** in 82% yield. Removal of the TBS group was achieved by treating compound **5** with PPTS (pyridinium paratoluene sulfonate) in MeOH, followed by oxidation of the



n = 2, (*E*)-norpatulolide C
n = 3, (*E*)-patulolide C
n = 4, (*E*)-homopatulolide C

n = 2, (*Z*)-norisopatulolide C
n = 3, (*Z*)-isopatulolide C
n = 4, (*Z*)-homoisopatulolide C

chloriolide

Scheme 1. Naturally occurring chloriolide and related macrolides.

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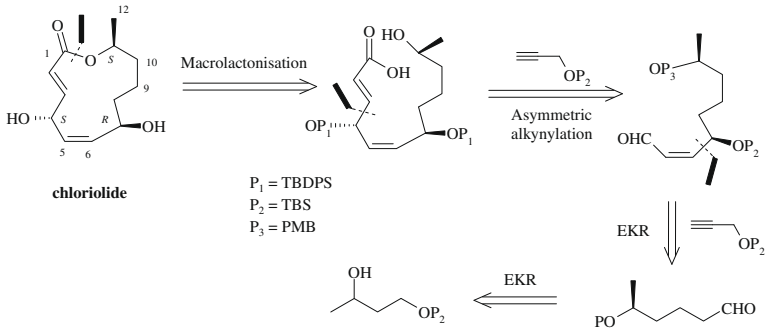
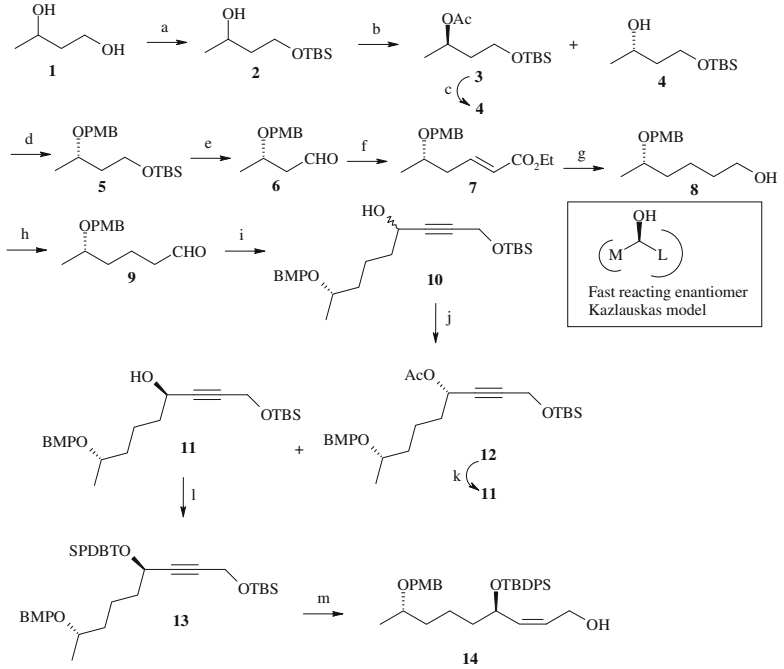


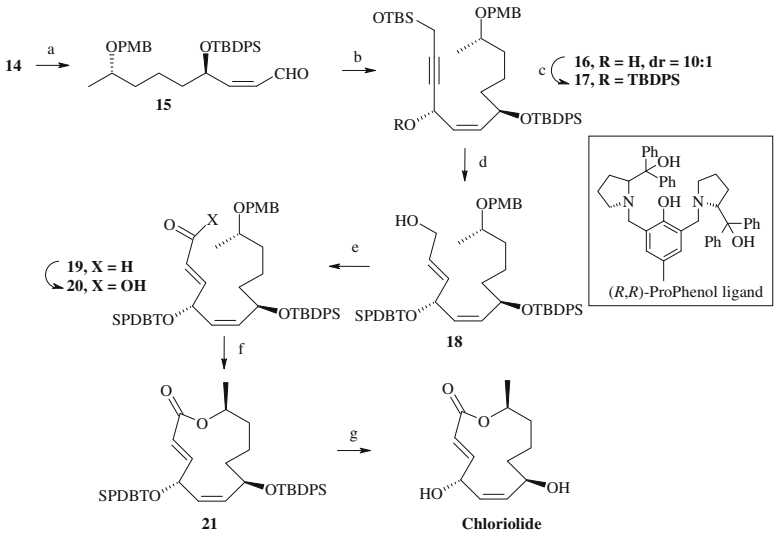
Scheme 2. Retrosynthetic analysis of chloriolide.

primary alcohol functionality under Swern condition[8] afforded the corresponding aldehyde **6** with 80% yield (in two steps). Then the aldehyde **6** was subjected to HWE (Horner–Wadsworth–Emmons) reaction with ethoxy carbonylmethylen-triphenylphosphorane to afford the α,β unsaturated ester **7** in 98% yield. The olefinic double bond in compound **7** was reduced by using $NiCl_2$, $NaBH_4$ in MeOH[9] to afford the corresponding saturated ester in 97% yield. Reduction of ester functionality was achieved by using $LiAlH_4$ in ether to afford the alcohol **8** in 88% yield. Swern oxidation of compound **8** afforded the desired aldehyde **9** in 80% yield. Then the aldehyde **9** was subjected to alkynylation reaction with the anion generated from TBS protected propargyl alcohol using *n*-BuLi as a base at −78 °C afforded the compound **10** in 80% yield. Compound **10** was obtained as mixtures of diastereomers. But we could not separate the diastereomers as their polarity remains same on TLC plate. Therefore we have decided to carry out a further round of EKR of compound **10** using CAL-B and vinyl acetate as the acyl donor. The transesterification reaction afforded the corresponding (*R*) alcohol **11** (yield = 47%) and (*S*) acetate **12** (yield = 48%) according to the Kazlauskas rule. Our required substrate was the slow reacting diastereomer **11** for the next synthetic steps. Hence the acetate **12** obtained from the fast reacting diastereomer was deacetylated and subjected to Mitsunobu inversion/hydrolysis protocol to afford the required diastereomeric alcohol **11** in 70% overall yield from **12**. The secondary alcohol functionality in **11** was protected as its TBDPS ether using imidazole and TBDPSCl (*tert*-butyldiphenylsilyl chloride) in DCM (dichloromethane) afforded the compound **13** in 80% yield. Selective removal of TBS group in the presence of TBDPS group was achieved by treating compound **13** with PPTS in MeOH,[10] afforded the corresponding propargylic alcohol in 70% yield. Then the acetylenic triple bond was converted to its corresponding *cis*(*Z*) double bond using Lindlar's catalyst under H_2 atmosphere with a small amount of quinoline afforded the compound **14** in 92% yield (Scheme 3).

Compound **14** was then oxidized to its corresponding (*Z*) aldehyde **15** by Dess–Martin periodinane (DMP) oxidation[11] in 85% yield. Aldehyde **15** was then subjected to asymmetric alkynylation protocol with *tert*-Butyl-dimethyl-prop-2-ynyloxy-silane by using (*R*,*R*)-pro-phenol catalyst developed by Trost et al.[12] to afford the compound **16** in 72% yield (dr = 10:1). The free secondary hydroxy group in **16** was protected as its TBDPS ether by treatment with imidazole and TBDPSCl at room temperature afforded the corre-



Scheme 3. Reagents and conditions. (a) NaH, THF, TBS-Cl, 90%; (b) CAL-B, DIPE, vinylacetate, 1 h; (c) (i) K_2CO_3/MeOH; (ii) Ph_3P/DIAD/AcOH; (iii) K_2CO_3/MeOH; (d) PMBO(C=NH)CCl_3, CSA, 82%; (e) (i) PPTS, MeOH; (ii) $(COCl)_2$, DMSO, Et_3N, −78 °C; (f) Ph_3P=$CHCO_2Et$, DCM, rt, 98%; (g) (i) $NiCl_2$, $NaBH_4$, MeOH, 97%; (ii) $LiAlH_4$, 45 min, 88%; (h) $(COCl)_2$, DMSO, Et_3N, −78 °C; (i) *tert*-butyl-dimethyl-prop-2-ynyloxy-silane, *n*-BuLi, −78 °C, 80%; (j) CAL-B, DIPE, vinylacetate, 72 h; (k) (i) K_2CO_3/MeOH; (ii) Ph_3P/DIAD/AcOH; (iii) K_2CO_3/MeOH, 70%; (l) TBDPS-Cl, imidazole, 90%; (m) (i) PPTS, MeOH, 78%; (ii) H_2, Lindlar's catalyst, 92%.



Scheme 4. Reagents and conditions. (a) Dess–Martin periodinane, 93%; (b) *tert*-butyl-dimethyl-prop-2-ynyloxy-silane, Me_2Zn, (*R*,*R*)-pro-phenol ligand, 72%; (c) TBDPS-Cl, imidazole, 88%; (d) (i) PPTS, MeOH; (ii) Red-Al, THF, −78 °C, 70% in two steps; (e) (i) DMP, DCM, 92%; (ii) NaH_2PO_4, $NaClO_2$, *t*-BuOH, 2-methyl-2-butene, H_2O, rt, 1 h, 92%; (f) (i) DDQ, DCM/H_2O (20:1), 78%; (ii) 2,4,6-trichlorobenzoylchloride, DIPEA (diisopropylethyl amine), DMAP, toluene 60 °C, 24 h, 64%; (g) NH_4F/MeOH, rt, 48 h, 55%.

sponding TBDPS ether **17** in 80% yield. Selective removal of the TBS ether was achieved by treating compound **17** with PPTS/MeOH followed by reducing the acetylenic triple bond to its corresponding trans double bond using red-Al{sodiumdihydro-bis(2-methoxyethoxy)aluminate)}[13] in THF afforded the compound **18** in 75% yield. Then this (*E*) alcohol **18** on oxidation using DMP in DCM afforded the corresponding (*E*) aldehyde **19** in 92% yield. Then the aldehyde **19** was converted to the corresponding acid **20** by Pinnic oxidation[14] in 70% yield (Scheme 4). Removal of PMB group was achieved by treating **20** with DDQ[15] in DCM/H_2O (20:1), to afford the *seco* acid in 78% yield. The hydroxyacid when subjected to macrolactonization reaction under Yamaguchi condition,[16] compound **21** was obtained in 64% yield. Removal of the TBDPS group in **21** was achieved by using NH_4F/MeOH to afford the target molecule chloriolide in 2.2% overall yield (Scheme 4).[17] The spectral characteristic values (^1H and ^{13}C NMR) of our synthesized chloriolide are in perfect agreement with those of the reported value in the literature.[1,18–29]

In conclusion we have reported the asymmetric synthesis of the 12-membered macrolide (+)-chloriolide in an efficient way. Enzymatic kinetic resolution/Mitsunobu inversion has been successfully employed to fix two of the hydroxy stereocenters (7*R* and 11*S*) in the target molecule. Whereas asymmetric alkynylation reaction by using Trost pro-phenol catalyst has been applied to fix the 4*S*-hydroxy stereocenter. Finally Yamaguchi macrolactonization of the properly functionalized *seco* acid afforded the target molecule.

Acknowledgments

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18. ^1H NMR of compound **6** (200 MHz, $CDCl_3$), δ: 9.76 (t, J = 2.4 Hz, 1H), 7.22 (d, J = 7.2 Hz, 2H), 6.9 (d, J = 7.2 Hz, 2H), 4.52 (d, J = 11.2 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 4.1 (m, 1H), 3.8 (s, 3H), 2.8–2.5 (m, 2H), 1.27 (d, J = 6.0 Hz, 3H). ^{13}C NMR (50 MHz), δ: 201.72, 159.48, 130.53, 129.51, 114.07, 70.51, 70.1, 55.5, 50.74, 20.05.
$[\alpha]_D^{25}$ +10.9 (*c* 1.0, $CHCl_3$).
19. ^1H NMR of compound **7** (200 MHz, $CDCl_3$), δ: 7.24 (d, J = 8.0 Hz, 2H), 7.1 (td, J = 16.0, 7.4 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 5.88 (td, J = 16.0, 2.8 Hz, 1H), 4.5 (d, J = 11.2 Hz, 1H), 4.39 (d, J = 11.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.8 (s, 3H), 3.66 (m, 1H), 2.5–2.3 (m, 2H), 1.3 (t, J = 7.2 Hz, 3H), 1.26 (d, J = 6.0 Hz, 3H).

^{13}C NMR (50 MHz), δ: 167.89, 159.33, 145.56, 130.79, 129.37, 123.55, 113.98, 73.41, 70.35, 60.38, 55.45, 39.47, 19.88, 14.46.
$[\alpha]_D^{25}$ +39.2 (*c* 1.0, $CHCl_3$).

20. ^{1}H NMR of compound **9** (200 MHz, $CDCl_3$), δ: 9.75 (t, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 3.84 (s, 3H), 3.5 (m, 1H), 2.5–2.4 (m, 2H), 1.8–1.4 (m, 4H), 1.28 (d, *J* = 6.4 Hz, 3H).
^{13}C NMR (50 MHz), δ: 202.67, 159.09, 130.96, 129.25, 113.77, 73.95, 70.0, 55.28, 43.81, 36.08, 19.53, 18.19.
$[\alpha]_D^{25}$ +9.2 (*c* 0.5, $CHCl_3$).
21. ^{1}H NMR of compound **11** (400 MHz, $CDCl_3$), δ: 7.25 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.36 (s, 2H), 4.34 (m, 1H), 3.79 (s, 3H), 3.50 (m, 1H), 1.6–1.5 m, 6H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.9 (s, 9H), 0.11 (s, 6H).
^{13}C NMR (100 MHz), δ: 159.08, 131.13, 129.21, 113.78, 85.88, 83.46, 74.40, 70.0, 62.39, 55.28, 51.74, 37.69, 36.24, 25.83, 21.21, 19.60, 18.30, −5.1.
$[\alpha]_D^{25}$ −11.06 (*c* 1.8, $CHCl_3$).
22. ^{1}H NMR of compound **14** (400 MHz, $CDCl_3$), δ: 7.66 (m, 4H), 7.5–7.3 (m, 6H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 5.44 (m, 1H), 5.34 (m, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.36 (m, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 3.78 (s, 3H), 3.59 (m, 2H), 3.4 (m, 1H), 1.6–1.3 (m, 6H), 1.18 d, *J* = 6.0 Hz, 3H), 1.0 (s, 9H).
^{13}C NMR (100 MHz), δ: 159.09, 130.68, 135.94, 134.59, 134.27, 131.05, 129.70, 129.63, 129.26, 128.53, 128.35, 127.58, 127.41, 113.76, 74.34, 69.98, 69.15, 58.51, 55.29, 37.99, 36.58, 26.99, 21.07, 19.64, 19.27.
$[\alpha]_D^{25}$ +3.1 (*c* 0.8, $CHCl_3$).
23. ^{1}H NMR of compound **15** (400 MHz, $CDCl_3$), δ: 9.34 (d, *J* = 2.2 Hz, 1H), 7.65 (m, 4H), 7.5–7.4 (m, 6H), 7.2 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.5 (m, 1H), 5.7 (dd, *J* = 11.2, 2.2 Hz, 1H), 4.94 (m, 1H), 4.45–4.32 (m, 2H), 3.82 (s, 3H), 3.45 (m, 1H), 1.8–1.3 (m, 6H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 9H).
^{13}C NMR (100 MHz), δ: 190.53, 159.09, 153.09, 135.87, 135.81, 133.42, 133.35, 131.06, 130.32, 129.99, 129.17, 128.31, 127.79, 127.71, 113.78, 74.23, 69.94, 69.02, 55.29, 37.95, 36.55, 26.97, 20.9, 19.55, 19.25.
$[\alpha]_D^{25}$ −4.8 (*c* 0.9, $CHCl_3$).
24. ^{1}H NMR of compound **16** (400 MHz, $CDCl_3$), δ: 7.66 (m, 4H), 7.45 (m, 6H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 5.5 (m, 1H), 5.3 (m, 1H), 4.5–4.4 (m, 4H), 4.25 (s, 2H), 3.78 (s, 3H), 3.44 (m, 1H), 1.6–1.4 (m, 6H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.0 (s, 9H), 0.88 (s, 9H), 0.1 (s, 6H).
^{13}C NMR (100 MHz), δ: 159.05, 136.09, 135.95, 134.64, 134.12, 134.03, 131.26, 129.82, 129.76, 129.13, 128.32, 127.66, 127.50, 113.77, 83.78, 83.63, 74.61, 70.04, 69.43, 58.17, 55.29, 51.65, 38.18, 36.60, 26.97, 25.81, 20.96, 19.63, 19.28, 18.24, −5.13.
$[\alpha]_D^{25}$ +77.2 (*c* 0.4, $CHCl_3$).
25. ^{1}H NMR of compound **18** (400 MHz, $CDCl_3$), δ: 7.66 (m, 8H), 7.5–7.2 (m, 14H), 6.88 (d, *J* = 8.0 Hz, 2H), 5.55 (m, 2H), 5.3 m, 1H), 4.94 (m, 1H), 4.6 (m, 1H), 4.5–4.3 (m, 3H), 3.77 (s, 3H), 3.6–3.4 (m, 3H), 1.4–1.2 (m, 6H), 1.2–1.0 (21H).
^{13}C NMR (100 MHz), δ: 159.08, 135.97, 135.83, 135.74, 134.79, 134.34, 134.23, 133.51, 132.73, 132.55, 131.17, 130.97, 130.83, 130.04, 129.91, 129.62, 129.47, 129.32, 129.19, 128.56, 127.46, 127.3, 126.97, 113.7, 74.62, 71.12, 69.9, 65.39, 62.55, 55.27, 38.42, 36.36, 36.19, 27.01, 26.89, 20.48, 19.5, 19.23.
$[\alpha]_D^{25}$ +11.26 (*c* 0.8, $CHCl_3$).
26. ^{1}H NMR of compound **19** (400 MHz, $CDCl_3$), δ: 9.08 (dd, *J* = 8.0, 3.6 Hz, 1H), 7.5 (m, 8H), 7.4–7.2 (m, 14H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.3 (td, *J* = 16, 5.2 Hz, 1H), 5.7 (m, 2H), 5.46 (m, 1H), 4.9 (m, 1H), 4.4 (d, *J* = 11.2 Hz, 1H), 4.32 (d, *J* = 11.2 Hz, 1H), 4.2 (m, 1H), 3.78 (s, 3H), 3.38 (m, 1H), 1.4–1.2 (m, 6H), 1.0 (21H).
^{13}C NMR (100 MHz), δ: 193.39, 158.93, 136.19, 135.77, 135.61, 135.28, 135.25, 134.73, 133.96, 133.77, 133.0, 132.98, 131.1, 130.03, 129.85, 129.77, 129.61, 129.54, 128.98, 128.6, 128.56, 127.62, 127.58, 127.46, 113.64, 74.33, 70.15, 69.9, 69.77, 55.21, 38.35, 36.57, 26.95, 26.71, 20.64, 20.47, 19.44, 19.13.
$[\alpha]_D^{25}$ +101.2 (*c* 0.5, $CHCl_3$).
27. ^{1}H NMR of compound **20** (400 MHz, $CDCl_3$), δ: 7.54 (m, 8H), 7.4–7.2 (m, 14H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.6 (td, *J* = 16.0, 5.6 Hz, 1H), 5.57 (m, 1H), 5.44 (m, 2H), 4.72 (m, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.1 (br, 1H), 3.78 (s, 3H), 3.33 (m, 1H), 1.4–1.3 (m, 6H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.0 (s, 18H).
^{13}C NMR (100 MHz), δ: 191.31, 158.9, 150.21, 135.74, 135.71, 135.69, 135.59, 135.13, 133.94, 133.89, 133.23, 132.99, 131.08, 129.79, 129.67, 129.49, 129.45, 129.06, 128.71, 127.56, 127.53, 127.43, 127.41, 118.98, 113.62, 74.45, 69.93, 69.81, 69.68, 55.19, 38.33, 36.34, 29.63, 26.93, 26.8, 20.53, 19.45, 19.39.
$[\alpha]_D^{25}$ +33.8 (*c* 1.0, $CHCl_3$).
28. ^{1}H NMR of compound **21** (400 MHz, $CDCl_3$), δ: 7.52–7.18 (m, 20H), 6.42 (dd, *J* = 16.0, 4.8 Hz, 1H), 5.7 (d, *J* = 16.0 Hz, 1H), 5.3–5.2 (m, 2H), 4.75 (m, 1H), 4.33 (m, 1H), 4.11 (m, 1H), 1.4–1.2 (m, 6H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.08 (s, 9H), 0.91 (s, 9H).
^{13}C NMR (100 MHz), δ: 166.7, 150.1, 135.81, 135.73, 135.68, 134.51, 133.9, 133.8, 133.42, 132.99, 131.58, 130.83, 129.78, 129.74, 129.57, 129.45, 128.74, 127.6, 127.41, 127.3, 119.94, 72.58, 71.27, 70.22, 35.72, 33.53, 29.64, 26.97, 20.99, 20.89, 19.22, 19.13.
$[\alpha]_D^{25}$ +92.1 (*c* 0.3, $CHCl_3$).
29. ^{1}H NMR of (+)-Chloriolide (400 MHz, $CDCl_3$), δ: 7.15 (dd, *J* = 15.8, 2.6 Hz, 1H), 6.12 (dd, *J* = 15.8, 2.6 Hz, 1H), 5.7–5.5 (m, 2H), 5.22 (m, 1H), 4.78 (m, 1H), 4.55 (m, 1H), 1.82–1.25 (m, 6H), 1.32 (d, *J* = 6.4 Hz, 3H).
^{13}C NMR (100 MHz), δ: 167.0, 152.7, 140.4, 126.9, 119.6, 74.2, 69.8, 68.3, 36.8, 34.5, 21.5, 19.7.
$[\alpha]_D^{25}$ +105.9 (*c* 0.2, $CHCl_3$). Lit $[\alpha]_D^{25}$ +107.0 (*c* 0.2, $CHCl_3$).