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Total synthesis of bioactive drimane–epoxyquinol hybrid natural products: macrophorin A, 4′-oxomacrophorin A, and 1′-*epi*-craterellin A

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ABSTRACT

Total synthesis of novel hybrid natural products, merosesquiterpenoids macrophorin A, 4′-oxomacrophorin A, and 1′-*epi*-craterellin A has been accomplished following a general strategy based on a sacrificial Diels–Alder–*retro*Diels–Alder approach to control regio- and stereoselectivity.

The virtuosity of nature in creating diverse molecular architecture while preserving the integrity of a particular biosynthetic pathway, for example, various terpenes from mevalonate derived geranyl pyrophosphate, farnesyl pyrophosphate, squalene oxide etc., is well recognized. However, sometimes nature also ventures to craft hybrid natural products[1] forged through the confluence of two distinct biosynthetic pathways. Such hybrid natural products are structurally distinct constructs and in many cases display unusual bioactivity profile. Understandably, such entities have not only drawn attention for total synthesis campaigns but also inspired efforts to explore new chemical space in the quest of drug-like NCE's.[1a,b,2]

Among the ever expanding canvas of hybrid natural products, drimanyl–epoxyquinols (merosesquiterpenoids) represented by framework **1**, and crafted through a union of mevalonate derived drimane (bicyclofarnesane) sesquiterpene framework (in red) and polyketide aromatic pathway derived epoxyquinol moiety (in blue) constitute a growing family of natural products.[3] Archetypal examples of drimanyl–epoxyquinols **2**–**8**, displaying functional group variation in both the drimane and epoxyquinol segments are displayed in Figure 1. Interestingly, quite a few of these hybrid natural products exhibit impressive and wide ranging bioactivities that include anti-fungal, anti-bacterial, anti-cancer, immunomodulatory, and strong toxicity against brine shrimp larvae among others.[3] For example, drimanyl–epoxyquinol natural products epoxyphomalin A **7a** and B **7b** exhibited impressive activity against several cancer cell lines at nanomolar concentration and it was also observed that these natural products exert their activity through inhibition of the 20S proteasome.[3f,i] Despite interesting structural features and bioactivities associated with drimanyl–epoxyquinol natural products and possibilities of exploring promising chemical space around them, we were surprised to find that no chemical synthesis of any member of this family has yet surfaced in the literature. Arising out of our long standing interest in the synthesis of epoxyquinol natural products,[4] we decided to enter the arena and wish to report here the first total synthesis of drimanyl–epoxyquinol natural products.

Macrophorin A **2a** was the first drimanyl–epoxyquinol natural product to be isolated and characterized[3a] in 1983 and since then its isolation has been repeatedly reported[3] from diverse sources. Natural product **2a** exhibited anti-bacterial activity against *staphylococcus aureus* (MIC 25 ppm) and anti-cancer activity against mouse tumor cell lines (L-5178Y) with IC_{50} of 0.3 ppm.[3a] In view of these attributes, we chose **2a** and its sibling **3** as our first targets for total synthesis. The synthetic strategy to **2a** and **3** was fairly straightforward and widely applicable and hinged on constructing the epoxyquinol moiety on a preformed drimane platform by harnessing the potential of a sacrificial Diels–Alder–*retro*Diels–Alder stratagem extensively explored by us[4] for regio- and stereoselective functionalization.

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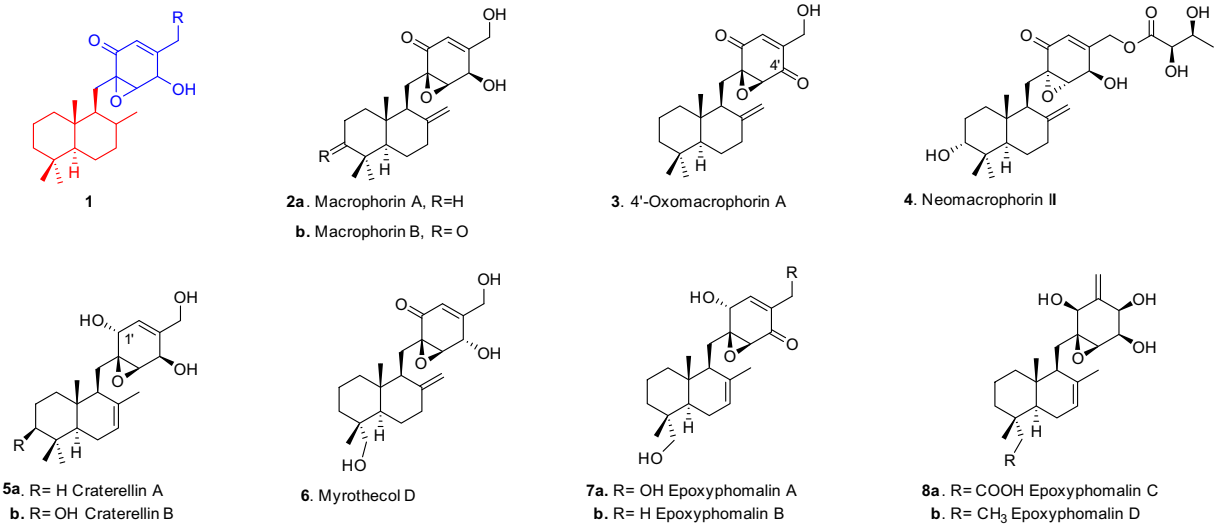
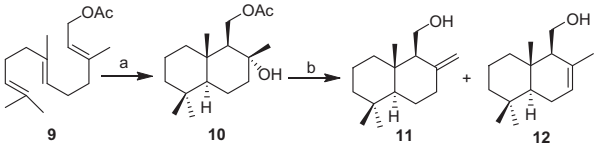
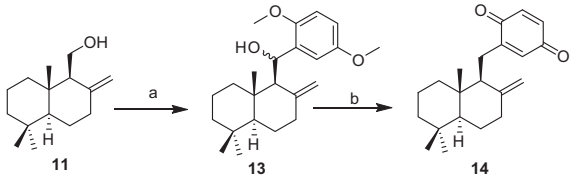


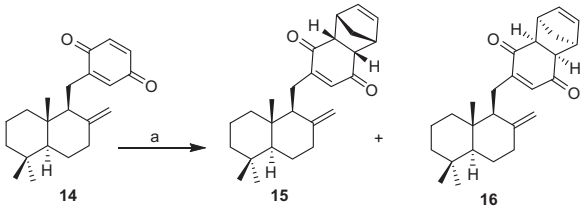
Figure 1. Representative examples of drimanyl–epoxyquinol hybrid natural products.



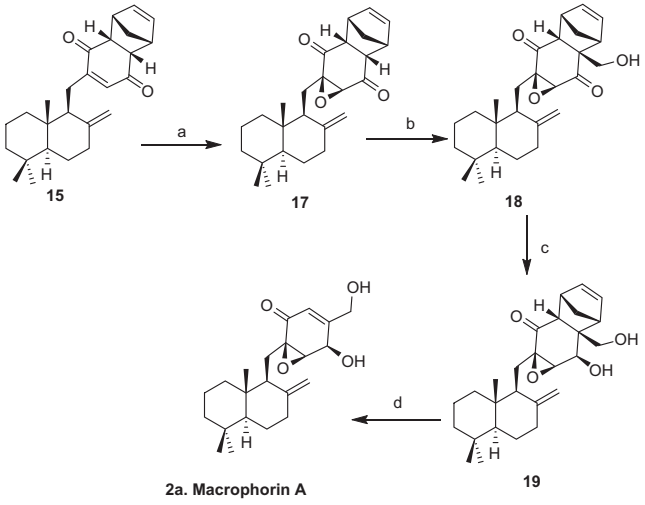
Scheme 1. Reagents and conditions: (a) $ClSO_3H$, 2-nitropropane, −78 °C, 30 min 60%; (b) (i) methanesulfonyl chloride (MsCl), Et_3N, THF, rt, 3 h; (ii) KOH, MeOH, 6 h, 90% (overall), **11**:**12** (1:1).



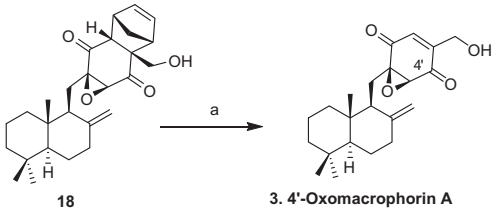
Scheme 2. Reagents and conditions: (a) (i) PCC, DCM, 30 min; (ii) *n*-BuLi, Et_2O, 2,5-dimethoxybromobenzene, −78 °C, 2 h, 87% (over two steps); (b) (i) Li, liq. NH_3, THF, 3 min 95%; (ii) CAN (ceric ammonium nitrate), $CH_3CN/H_2O/Et_2O$ (1:1:0.5), 15 min, 52%.



Scheme 3. Reagents and conditions: (a) cyclopentadiene, $MeOH/Et_2O$ (1:1), 0 °C, 4 h, 85% (overall), 59% (for **15**) **15**:**16** (7:3).

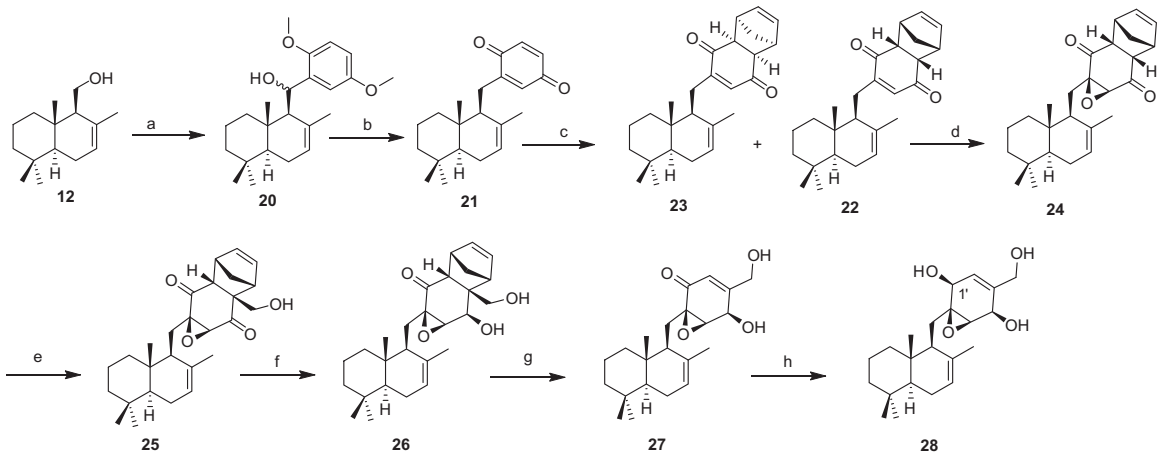


Scheme 4. Reagents and conditions: (a) H_2O_2; 10% Na_2CO_3, 4 h, rt, 90%; (b) HCHO, DBU, THF, 0 °C, 5 h, 96%; (c) DIBALH, THF, −78 °C, 3 h, 92%; (d) Ph_2O, 240 °C, 15 min, 89%.



Scheme 5. Reagents and conditions: (a) Ph_2O, 240 °C, 15 min, 85%.

Farnesyl acetate **9** was subjected to polyene cyclization in chlorosulfonic acid following a reported protocol[5] to deliver the bicyclic drimane (bicyclofarnesane) derivative **10** which upon dehydration and hydrolysis led to a readily separable mixture (1:1) of drimanols **11** and **12**, Scheme 1. Both **11** and **12** were considered serviceable since drimanyl–epoxyquinol natural products are encountered in exocyclic and endocyclic double bond bearing variants, (see Fig. 1). Pyridinium chlorochromate (PCC)-mediated oxidation of the primary hydroxyl group in **11** to the aldehyde and addition of lithiated 2,5-dimethoxybromobenzene led to **13** which was directly subjected to sequential reductive deoxygenation[6] and ceric ammonium nitrate (CAN) oxidation to deliver



Scheme 6. Reagents and conditions: (a) (i) PCC, DCM, 30 min; (ii) *n*-BuLi, Et_2O, 2,5-dimethoxybromobenzene, −78 °C, 2 h, 79% (over two steps); (b) (i) Li, liq. NH_3, THF, 3 min 98%; (ii) CAN (ceric ammonium nitrate), $CH_3CN/H_2O/Et_2O$ (1:1:0.5), 15 min, 50%; (c) cyclopentadiene, MeOH/Et_2O (1:1), 0 °C, 4 h, 85% (overall), 59% (for **22**) **22**:**23** (7:3); (d) H_2O_2; 10% Na_2CO_3, 4 h, rt, 84%; (e) HCHO, DBU, THF, 0 °C, 5 h, 98%; (f) DIBAL-H, THF, −78 °C, 3 h, 97%; (g) Ph_2O, 240 °C, 15 min, 85%; (h) DIBALH, THF, −78 °C, 3 h, 99%.

the requisite benzoquinone derivative **14**, Scheme 2, and set the stage for the implementation of the sacrificial Diels–Alder–*retro*-Diels–Alder steps, concomitant with the generation of the oxygenation pattern of the epoxyquinol segment.

The Diels–Alder reaction between **14** and cyclopentadiene furnished two diastereomeric *endo*-adducts **15** and **16** in 7:3 ratio.[7] The underlying reasons for the observed face selectivity in the Diels–Alder reaction leading to **15** and **16** cannot be explained by steric factors alone and perhaps reflect a cumulative expression of the prevailing stereoelectronic environment.[8] However, it was gratifying that the required diastereomer **15** predominated, Scheme 3.

Nucleophilic epoxidation of **15**, as expected and planned was stereoselective, engendered by the *exo*-face selectivity of the norbornyl scaffold present in it, to deliver **17**. α-Hydroxymethylation in **17** to introduce the side arm was regioselective and guided by our previous observations in similar systems.[4b,c] The resulting **18** was now subjected to controlled diisobutylaluminum hydride (DIBALH) reduction which pleasingly turned out to be regio- and stereoselective with the hydride attacking the carbonyl group from the less encumbered *endo* (α) face to deliver **19** with the requisite hydroxyl stereochemistry. The stage was now set to disengage the sacrificial cyclopentadiene moiety and the *retro*Diels–Alder reaction in **19** was smoothly implemented through thermal activation to deliver macrophorin A **2a**, Scheme 4. The spectral characteristics (^{1}H NMR, ^{13}C NMR) of our synthetic **2a** were identical with those reported for the natural product.[3a,l,7]

When **18** was directly subjected to thermal activation to effect the *retro*Diels–Alder reaction, natural product 4′-oxomacrophorin A **3** was obtained, (Scheme 5) and identified by comparison of its spectral data (^{1}H NMR, ^{13}C NMR) with the natural product.[3e,7]

We have indicated (vide supra) that both the bicyclic drimanols **11** and **12** obtained from the polyene cyclization of farnesyl acetate **9** were deployable for the synthesis of drimane–epoxyquinol hybrid natural products. Having demonstrated the utility of the exocyclic drimanol isomer **11** in the total synthesis of macrophorins, we ventured to explore the possibilities with endocyclic drimanol **12** following a similar tactic. For a preliminary foray, more recently isolated[3g] craterellin A **5a** was selected as the potential target for synthesis, particularly as it was shown to exhibit inhibitory activity against two isozymes of 11β-hydroxysteroid dehydrogenase (11β-HSD1 and 11β-HSD2) with wide therapeutic implications including in obesity and diabetes.[3g,3j]

The benzoquinone moiety was appended to drimanol **12** via PCC-oxidation, addition of the organolithium reagent derived from 2,5-dimethoxybromobenzene, and CAN oxidation to furnish **20**, Scheme 6. The Diels–Alder reaction of the quinone moiety in **20** with cyclopentadiene once again furnished a mixture (7:3) of diastereomeric *endo* adducts **22** and **23** and the former was processed further. Nucleophilic epoxidation leading to **24** was stereoselective and further regio- and stereoselective hydroxymethylation eventuated in **25**, Scheme 6. A regio- and stereoselective carbonyl reduction of **25** led to **26**. As planned, *retro*Diels–Alder reaction in **26** was uneventful and delivered 1′-oxo-craterellin A **27** and its formulation was fully secured through single crystal X-ray structure determination.[9] At this stage, what awaited the completion of the total synthesis of **5a** was a stereoselective reduction of the carbonyl group in **27** from the top face, Scheme 6. However, reduction of the carbonyl group in **27** using different reagents (DIBALH, $NaBH_4$ etc.) and reaction conditions was highly stereoselective in a devious sense and only delivered 1′-*epi*-craterellin A **28** with hydride delivery from the α-face. Its formulation was secured through X-ray crystal structure determination of its tri-*p*-bromobenzoate derivative.[10] Thus, synthetic access to the natural product craterellin A **5a** eluded us at the last step due to the unexpected and somewhat inexplicable stereochemical outcome during the hydride reduction step. Nonetheless, in the overall sense it reinforced the validity of our conceptualization of a short access to drimanyl–epoxyquinol natural products.

In conclusion, we have outlined a short, general, and diversity oriented approach toward bioactive drimanyl–epoxyquinol hybrid natural products from commercially available farnesol employing a Diels–Alder–*retro*Diels–Alder strategy as a regio- and stereocontrol element.

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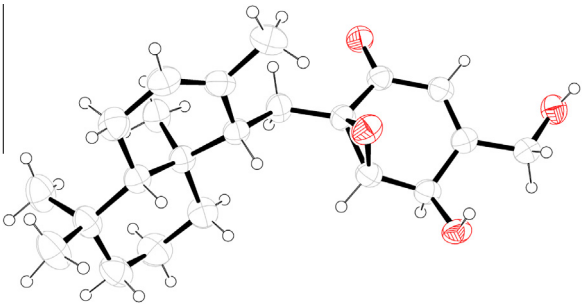
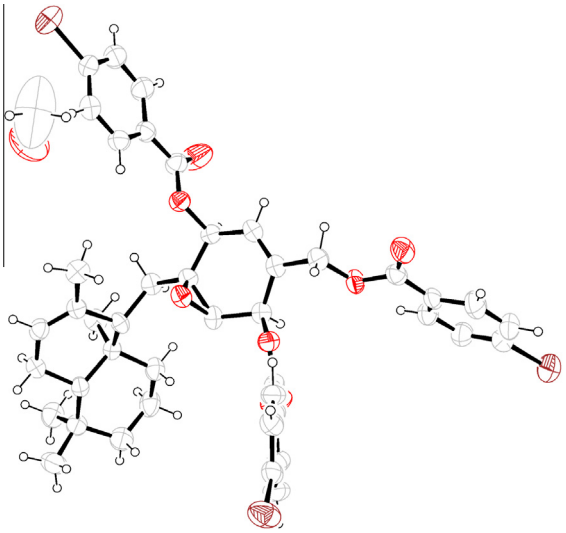
7. All compounds reported here are racemic and were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectral data. Spectral data of selected compounds are given here: compound **15**: IR ($CHCl_3$) 2920, 2854, 1753, 1752, 1665, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 6.00 (s, 1H), 5.95 (s, 1H), 4.74 (s, 1H), 4.26 (s, 1H), 3.49 (br s, 2H), 3.21-3.17 (m, 2H), 2.47 (br s, 2H), 2.34 (d, J = 12 Hz, 1H), 1.98–1.89 (m, 2H), 1.74–1.06 (m, 10H), 0.87 (s, 3H), 0.81 (s, 3H), 0.74(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.65, 199.36, 155.62, 147.32, 139.21, 135.47, 134.84, 107.94, 55.57, 54.41, 49.08, 48.91, 48.79, 48.70, 48.50, 42.00, 39.83, 39.15, 37.90, 33.61, 24.23, 23.67, 21.70, 19.34, 14.51; HRMS (ESI): calcd 379.2632 (M+H)$^+$; found 379.2637; melting point: 124–127 °C; compound **17**: IR ($CHCl_3$) 2920, 2860, 1709, 1446 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (s, 2H), 4.81 (d, J = 1.0 Hz, 1H), 4.40 (s, 1H), 3.44 (dq, J = 11.0, 3.5 Hz, 2H), 3.37 (s, 1H), 3.30 (s, 1H), 3.27 (s, 1H), 2.42–2.39 (m, 1H), 3.32 (dd, J = 15.5, 11.0 Hz, 1H), 2.08–2.00 (m, 2H), 1.73–1.72 (m, 1H), 1.68–1.66 (m, 1H), 1.59 (s, 1H), 1.53–1.47 (m, 3H), 1.43–1.37 (m, 1H), 1.33–1.27 (m, 2H), 1.25–1.21 (m, 1H), 1.09 (dd, J = 13.0, 2.5 Hz, 1H), 1.01-0.95 (m, 1H), 0.88 (s, 3H), 0.81(s, 3H), 0.76(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.55, 205.28, 149.26, 136.62, 136.58, 106.58, 66.49, 62.79, 55.47, 51.37, 50.55, 49.93, 46.67, 43.42, 43.13, 42.01, 39.32, 39.16, 37.73, 33.58, 33.53, 24.17, 21.66, 20.01, 19.27, 14.56; HRMS (ESI): calcd 417.2400 (M+Na)$^+$; found 417.2407; Melting Point: 130–134 °C; compound **18**: IR ($CHCl_3$) 3386, 2953, 2926, 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (br s, 2H), 4.78 (s, 1H), 4.39 (s, 1H), 4.34 (d, J = 11.2 Hz, 1H), 3.78 (d, J = 14.0 Hz, 1H), 3.43 (s, 1H), 3.32 (s, 1H), 3.28 (s, 1H), 2.85 (d, J = 4.5 Hz, 1H), 2.39–2.37 (m, 1H), 2.5–2.2 (m, 1H), 2.11–2.07 (m, 1H), 2.10–1.94 (m, 2H), 1.75–1.4 (m, 7H), 1.35–1.25 (m, 2H), 1.22–1.13 (m, 1H), 1.10–1.04 (m, 1H), 0.88 (s, 3H), 0.80 (s, 3H), 0.7 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.74, 204.64, 148.95, 138.12, 137.89, 106.74, 68.18, 67.53, 62.50, 61.47, 55.48, 53.73, 51.23, 45.92, 44.53, 43.42, 41.98, 39.40, 39.13, 37.78, 33.59, 33.00, 24.16, 21.67, 19.90, 19.26, 14.55; HRMS (ESI): calcd 447.2506 (M+Na)$^+$; found 447.2513; compound **19**: IR ($CHCl_3$) 3342, 2926, 2865, 1704, 1643, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 6.13 (s, 1H), 4.77 (s, 1H), 4.64 (d, J = 8.8 Hz, 1H), 4.42 (s, 1H), 4.06 (s, 1H), 3.94 (s, 1H), 3.82 (d, J = 8.8 Hz, 1H), 3.45 (s, 1H), 3.29 (s, 1H), 3.24 (s, 1H), 2.86 (br s, 1H), 2.51–2.50 (m, 1H), 2.40–2.38 (m, 1H), 2.16–2.11 (m, 1H), 2.02–1.96 (m, 2H), 1.74–1.68 (m, 2H), 1.68–1.48 (m, 4H), 1.37–1.25 (m, 2H), 1.23–1.09 (m, 2H), 0.95–1.07 (m, 1H), 0.88 (s, 3H), 0.80 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.12, 149.34, 140.33, 135.95, 106.64, 73.10, 70.11, 66.97, 63.45, 55.49, 55.10, 51.35, 50.92, 46.67, 44.42, 44.20, 42.07, 39.41, 39.08, 37.90, 33.58, 33.55, 24.23, 21.67, 19.81, 19.31, 14.52; HRMS (ESI): calcd 449.2662 (M+Na)$^+$; found 449.2669; Compound **2a** (macrophorin A): IR ($CHCl_3$) 3364, 2926, 1855, 1715, 1682, 1463 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 5.91 (d, J = 1.5 Hz, 1H), 4.77 (s, 1H), 4.56 (s, 2H), 4.29 (d, J = 15.0 Hz, 1H), 4.21 (d, J = 15.0 Hz, 1H), 3.67 (d, J = 2.5 Hz, 1H), 2.33–2.30 (m, 2H), 1.92 (td, J = 15.0, 5.0 Hz, 1H), 1.82 (dd, J = 14.0, 11.5 Hz, 1H), 1.75–1.73 (m, 3H), 1.62–1.56 (m, 1H), 1.52–1.46 (m, 1H), 1.41–1.35 (m, 1H), 1.32–1.26 (m, 1H), 1.22–1.18 (m, 2H), 1.12 (dd, J = 13.0, 2.5 MHz, 1H), 0.85 (s, 3H), 0.79 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 195.51, 161.13, 150.61, 120.37, 107.38, 66.22, 62.36, 62.20, 61.30, 56.94, 52.96, 43.31, 40.74, 40.02, 39.26, 34.52, 34.03, 25.66, 22.11, 20.41, 15.00; HRMS (ESI): calcd 383.2193 (M+Na)$^+$; found 383.2198; compound **3** (4′-oxomacrophorin A): IR ($CHCl_3$) 3441, 2926, 2849, 1687, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 4.81 (s, 1H), 4.52 (d, J = 19.2 Hz, 1H), 4.49 (s, 1H), 4.35 (d, J = 19.1 Hz, 1H), 3.72 (s, 1H), 2.46 (d, J = 14.8 Hz, 1H), 2.35 (br d, J = 12.8 Hz, 1H), 2.00 (dd, J = 16.0, 11.2 Hz, 2H), 1.93–1.88 (m, 1H), 1.68 (d, J = 12.0 Hz, 2H), 1.75–1.70 (m, 1H), 1.57–1.53 (m, 2H), 1.40–1.35 (m, 1H), 1.30–1.28 (m, 1 H), 1.20–1.13 (m, 1H), 1.10 (br d, J = 12.0 Hz, 1H), 0.86 (s, 3H), 0.78 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.55, 191.97, 148.77, 146.74, 132.14, 106.89, 62.55, 59.27, 59.12, 55.56, 51.50, 42.03, 39.80, 38.94, 38.05, 33.62, 33.52, 24.39, 21.65, 20.32, 19.34, 14.47; HRMS (ESI): calcd 381.2036 (M+Na)$^+$; found 381.2046; compound **22**: IR ($CHCl_3$) 2958, 2926, 2854, 1736, 1676, 1468 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.08–6.03 (m, 2H), 5.41 (s, 1H), 3.55 (d, J = 12.0 Hz, 2H), 3.24–3.23 (m, 2H), 2.43 (dd, J = 16.9, 9.6 Hz, 1H), 2.29–2.25 (m, 1H), 2.09 (s, 1H), 2.03–1.95 (m, 1H), 1.91–1.81 (m, 1H), 1.78–1.69 (m, 2H), 1.58–1.52 (m, 2H), 1.45 (s, 3H), 1.49–1.39 (m, 2H), 1.25–1.14 (m, 2H), 1.02 (dt, J = 13.0, 3.8 Hz, 1H), 0.89 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.20, 199.15, 157.80, 139.23, 135.56, 135.24, 133.70, 123.33, 53.33, 50.11, 48.87, 48.80, 48.78, 48.67, 48.37, 43.68, 42.10, 39.66, 36.87, 33.17, 33.02, 26.48, 23.07, 22.71, 21.86, 18.82, 13.81; HRMS (ESI): calcd 401.2451 (M+Na)$^+$; found 401.2459; compound **24**: IR ($CHCl_3$) 2964, 2920, 2854, 1720, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 2H), 5.44 (s, 1H), 3.49 (t, J = 2.6 Hz, 2H), 3.36 (s, 1H), 3.30 (d, J = 8.8 Hz, 2H), 2.25 (dd, J = 16.1, 8.8 Hz, 1H), 1.99 (d, J = 18.3 Hz, 1H), 1.89–1.85 (m, 2H), 1.68 (d, J = 13.2 Hz, 1H), 1.58 (s, 3H), 1.55–1.49 (m, 2H), 1.45–1.39 (m, 2H), 1.35–1.30 (m, 3H), 1.20–1.10 (m, 2H), 0.88 (s, 3H), 0.86 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.52, 205.34, 136.73, 136.58, 133.69, 122.88, 66.13, 61.63, 50.64, 50.34, 49.95, 47.09, 46.67, 43.34, 43.10, 42.11, 39.44, 35.94, 33.09, 32.96, 23.70, 22.43, 21.78, 21.68, 18.66, 13.71; HRMS (ESI) calcd 417.2400 (M+Na)$^+$; found 417.2412; compound **25**: IR ($CHCl_3$) 3408, 2958, 2920, 2854, 1709, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 2H), 5.41 (s, 1H), 4.40 (d, J = 10.5 Hz, 1H), 3.8 (d. J = 11.4 Hz, 1H), 3.42 (s, 1H), 3.35-3.27 (m, 2H), 2.88–2.87 (m, 1H), 2.27–2.21 (m, 1H), 2.10–2.04 (m, 1H), 2.02–1.90 (m, 1H), 1.90–1.80 (m, 1H), 1.70–1.60 (m, 2H), 1.53 (s, 3H), 1.50–1.37 (m, 5H), 1.25–1.21 (m, 1H), 1.15–1.12 (m, 2H), 0.85 (s, 3H), 0.84 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.59, 204.62, 138.27, 137.85, 133.56, 122.94, 68.20, 67.18, 61.69, 61.36, 54.22, 49.98, 47.02, 45.77, 44.29, 43.36, 42.10, 39.48, 35.95, 33.09, 32.96, 23.70, 22.13, 21.75, 18.64, 13.69; HRMS (ESI): calcd 447.2506 (M+Na)$^+$; found 447.2512; compound **27**: IR ($CHCl_3$) 3391, 2920, 2849, 1676, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.43 (s,1H), 4.75 (s, 1H), 4.45 (s, 2H), 3.75 (d, J = 2.9 Hz, 1H), 2.80 (s, 1H), 2.31 (dd, J = 15.7, 9.5 Hz, 1H), 2.03–1.96 (m, 1H), 1.90–1.80 (m, 2H), 1.79–1.66 (m, 2H), 1.60 (s, 3H), 1.58–1.41 (m, 3H), 1.32–1.12 (m, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.22, 156.06, 134.43, 122.50, 121.19, 65.80, 63.01, 60.39, 58.07, 50.08, 46.73, 42.22, 39.54, 36.21, 33.12, 33.00, 23.77, 21.97, 21.81, 21.54, 18.76, 13.79; HRMS (ESI): calcd 383.2187 (M+Na)$^+$; found 383.2199; melting point: 174-178 °C; compound **28**: IR ($CHCl_3$) 3369, 2926, 2865, 1671, 1452 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 5.53–5.52 (m, 1H), 5.4 (s, 1H), 4.65 (br s, 2H), 4.40 (s, 1H), 4.31 (s, 1H), 4.23 (d, J = 13.9 Hz, 1H), 4.09 (d, J = 13.9 Hz, 1H), 3.37 (d, J = 2.8 Hz, 1H), 2.13 (d, J = 15.0 Hz, 1H), 2.05–1.97 (m, 1H), 1.94–1.79 (m, 3H), 1.73 (s, 3H), 1.71–1.67 (m, 1H), 1.64–1.55 (m, 1H), 1.52–1.43 (m, 2H), 1.27–1.22(m, 2H), 1.08–1.00 (m, 1H), 0.93 (s, 3H), 0.89 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 138.02, 136.66, 124.91, 123.04, 68.27, 66.29, 63.19, 62.98, 60.97, 51.73, 43.63, 40.67, 37.72, 34.08, 33.82, 29.45, 24.97, 23.11, 22.41, 20.00, 14.30; HRMS (ESI): calcd 385.2349 (M+Na)$^+$; found 385.2357.
8. For a discussion on face selectivity during Diels–Alder reactions, see: Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278–286.
9. *Crystal data for* **27***:* Single crystal X-ray diffraction data for **27** was collected on Oxford CCD X-ray diffractometer (Yarnton, Oxford, UK) equipped with Cu-Kα radiation (λ = 1.54 Å) source. The data were reduced by *SAINTPLUS*; an empirical absorption correction was applied using the package *SADABS* and *XPREP* was used to determine the space group. The crystal structure was solved by direct methods using *SIR92* and refined by the full-matrix least-squares method on F^2 using *SHELXL97*. Crystal data: $C_{22}H_{32}O_4$, M = 360.48, monoclinic, *P1 21/c 1*, a = 22.3524(12), b = 7.5163(3), c = 12.0589(5) Å, V = 1988.76(16) Å^3, Z = 4, ρ_{calcd} = 1.204 mg/m^3, reflections collected/unique = 6616/3539 [R(int) = 0.0228], R_1 = *0.0739 and* wR_2 = *0.2090*, CCDC no. 984116. An ORTEP diagram of **27**, drawn at 35% ellipsoidal probability, is shown below:





10. Crystal data for tri-*p*-bromobenzoate derivative of **28** was collected on a Bruker AXS SMART APEX CCD diffractometer at 291 K using graphite monochromated MoK_{α} radiation ($\lambda = 0.7107$ Å). The data were reduced by *SAINTPLUS*; an empirical absorption correction was applied using the package *SADABS* and *XPREP* was used to determine the space group. The crystal structure was solved by direct methods using *SIR92* and refined by the full-matrix least-squares method on F^2 using *SHELXL97*. Crystal data: $C_{44}H_{44}Br_3O_8$, $M = 940.52$, monoclinic, *P2(1)/c*, $a = 15.6212(18)$, $b = 10.6145(12)$, $c = 26.395(3)$ Å, $V = 4228.3(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.477$ g/cm^3, 8713 reflections measured, 3786 unique ($R_{int} = 0.0798$), $R_1 = 0.0618$ and $wR_2 = 0.1514$, CCDC no. 1015321. An ORTEP diagram of tri-*p*-bromobenzoate derivative of **28**, drawn at 35% ellipsoidal probability, is shown below: