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Olefin cross-metathesis in the preparation of polycyclopropanes: formal synthesis of FR-900848

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Abstract

Olefin cross-metathesis was used for the efficient incorporation of an *E*-olefin between two cyclopropane residues. The generation of a bis-cyclopropyl alkene homodimer, followed by cross metathesis with a terminal vinyl polycyclopropane, provided excellent yields of the targeted compounds with good olefin stereoselectivity. The strategy was applied to generation of a quinta-cyclopropane intermediate found in a previous synthesis of the natural product FR-900848. © 2000 Elsevier Science Ltd. All rights reserved.

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The isolation and identification of two polycyclopropanated natural products has inspired numerous synthetic efforts directed toward the assembly of these challenging molecular targets. Both (–)-FR-900848 (**1**) and (–)-U-106305 (**2**) possess an unprecedented assembly of contiguous cyclopropanes located on a fatty amide backbone (Fig. 1). The remarkable structural similarity of these compounds stands in contrast to their divergent biological activities. (–)-FR-900848 (**1**) was isolated from *Streptovercillium fervens* and was demonstrated to possess remarkably specific biological activity with respect to its inhibition of non-filamentous fungi.[1] In contrast to the antifungal activity of **1**, (–)-U-106305 was identified by Upjohn in a screen for inhibitors of cholesteryl ester transfer protein (CEPT).[2] Efforts to develop a clear structure–activity profile will require the evolvement of efficient stereoselective approaches to these polycyclopropanated skeletons. Most of the reported approaches toward these skeletons have focused on the stereocontrolled formation of the contiguous cyclopropanes;[3–7] however, the non-conjugated (Δ_{14}) *E*-alkene also presents its share of synthetic challenges. More specifically, the location of the alkene between two cyclopropane units limits the options available for olefin formation.

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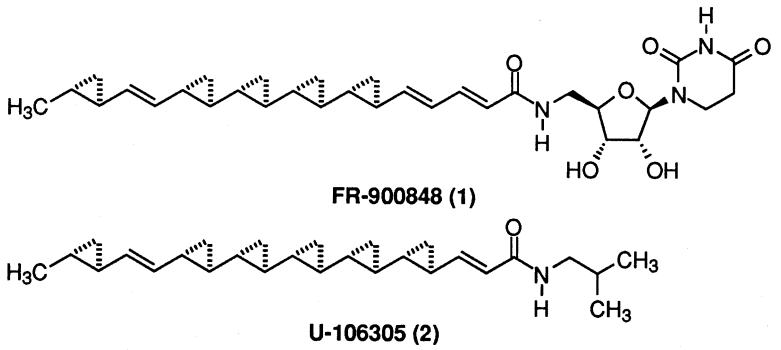
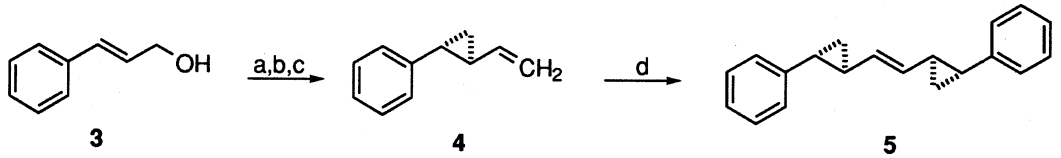


Figure 1.

A number of approaches to the stereoselective formation of an *E*-alkene flanked by two cyclopropane moieties have been described. These methods include Whitham elimination,[8] hydroxyl-directed mono-cyclopropanation of an *E,E*-dienol,[5] sulfone-modified Peterson olefination, followed by dissolving metal desulfurization,[6] and a modified Julia coupling strategy.[7] Poor yields, additional synthetic steps for the removal of extraneous functionality, or modest olefin selectivity plague many of these approaches; therefore, an alternative stereoselective approach to the dicyclopropyl ethylene moiety is desired.

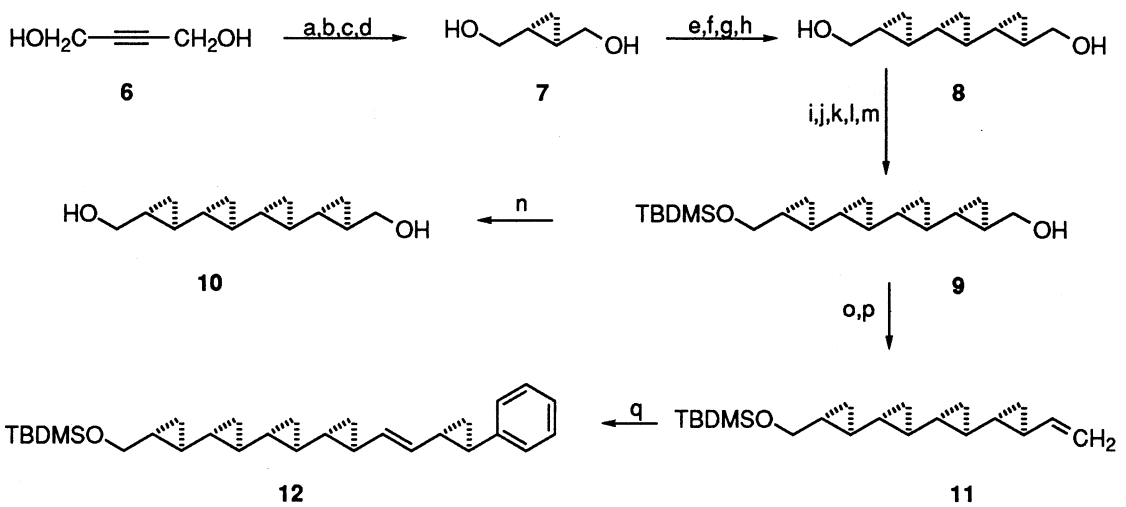
We contemplated the application of an olefin metathesis reaction.[9] Olefin metathesis has quickly become an attractive method for the assembly of complex functionality due to its power, operational simplicity, and tolerance of a wide range of functional groups; however, application of olefin metathesis to intermolecular cross-coupling reactions has been limited. Nevertheless, we envisioned the application of the olefin cross-metathesis reaction reported by Grubbs[10] to the formation of the Δ_{14}-*E*-alkene found in the two polycyclopropanated natural products. The absence of reactive intermediates and the expectation of good *E*-selectivity were desirable features of this method.

In order to test the compatibility of an olefin cross-metathesis strategy to the formation of alkenes flanked by cyclopropanes, cinnamyl alcohol **3** was converted to the optically active cyclopropane (89% ee)[11] (Scheme 1) through the influence of a D-tartrate-derived dioxaboralane.[12] Oxidation with TPAP/NMO[13] and olefination with triphenylphosphonium methylide provided vinyl cyclopropane **4**. The exposure of **4** to Grubbs' catalyst ($(Cy_3P)_2Cl_2Ru{=}CHPh$) in refluxing methylene chloride provided the homodimer **5** (62%, 6:1; *E*:*Z*).[14]



Scheme 1. (a) Et_2Zn, CH_2I_2, D-tartrate-derived dioxaboralane, 98%; (b) TPAP, NMO; (c) Ph_3PCH_3Br, CH_3Li, 83% for two steps; (d) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (5 mol%), 62%

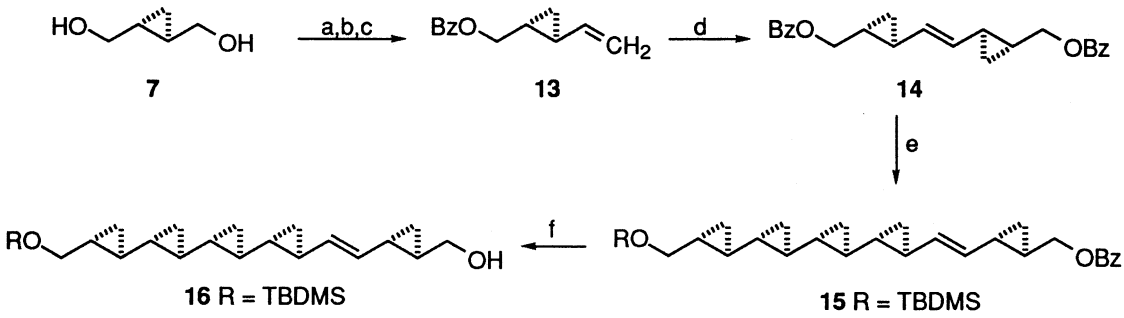
The polycyclopropanated cross-metathesis partner was prepared in the fashion similar to that previously reported by our group (Scheme 2).[15] Reduction of butyne-1,4-diol **6** with lithium aluminum hydride was followed by mono-protection with *t*-butyldimethylsilyl chloride (TBDMSCl) and triethylamine. The allylic alcohol was exposed to D-tartrate-derived dioxaboralane-directed cyclopropanation conditions, which upon removal of the silyl protecting group provided the *trans*-(1*R*,2*R*)-bis-hydroxymethylcyclopropane **7**.[15] Both alcohol functionalities were oxidized and the dialdehyde chain-extended in two directions using a Horner–Emmons reaction. Following reduction with excess DIBAL-H, the bis-allylic alcohol was exposed to D-tartrate-derived dioxaboralane-directed cyclopropanation conditions to provide bis-hydroxymethyl-*tris*-cyclopropane **8**. Mono-protection of **8** with TBDMSCl and triethylamine, followed by oxidation and chain extension provided an α,β-unsaturated ester, which was reduced with excess DIBAL-H. Cyclopropanation of the allylic alcohol was once again directed by D-tartrate-derived dioxaboralane to provide *tetrakis*-cyclopropane **9**. The removal of the protecting group with tetra-*n*-butylammonium fluoride (TBAF) confirmed the anticipated C_2-symmetry of bis-hydroxymethyl-*tetrakis*-cyclopropane **10** (87% ee).[15] Oxidation of **9**, followed by olefination with triphenylphosphonium methylide provided vinyl-*tetrakis*-cyclopropane **11** in high yield. The vinyl-*tetrakis*-cyclopropane **11** and two equivalents of the homodimer **5** were combined and exposed to Grubbs' catalyst in refluxing methylene chloride for 20 hours. Following chromatographic purification, the phenyl analog **12** of the polycyclopropanated side chain was formed in excellent yield (94%)[16] as a mixture of *E*- and *Z*-olefins (3.5:1).[17]



Scheme 2. (a) $LiAlH_4$, 79%; (b) TBDMSCl, Et_3N (1 equiv.), 86%; (c) Et_2Zn, CH_2I_2, D-tartrate-derived dioxaboralane; (d) AcOH/THF/H_2O (1:1:1), 86% for two steps; (e) TPAP, NMO; (f) $(EtO)_2P(O)CH_2CO_2Et$, NaH, 78% for two steps; (g) DIBAL-H, 73%; (h) Et_2Zn, CH_2I_2, D-tartrate-derived dioxaboralane, 60%; (i) TBDMSCl, Et_3N (1 equiv.), 68%; (j) TPAP, NMO; (k) $(EtO)_2P(O)CH_2CO_2Et$, NaH, 92% two steps; (l) DIBAL-H, 53%; (m) Et_2Zn, CH_2I_2, D-tartrate-derived dioxaboralane, 95%; (n) *n*-Bu_4NF, 67%, 87% ee; (o) TPAP, NMO; (p) Ph_3PCH_3Br, CH_3Li, 75% for two steps; (q) **5** (two equiv.), $(Cy_3P)_2Cl_2Ru$=CHPh (5 mol%), 94%

Successful olefin cross-metathesis in the formation of **12** encouraged its application toward FR-900848 (**1**). The preparation of an intermediate that would constitute a formal synthesis of FR-900848 was envisioned (Scheme 3). Mono-protection of bis-hydroxymethylcyclopropane **7** with benzoyl chloride (BzCl), followed by oxidation and olefination provided vinyl cyclopropane

13. The exposure of **13** to Grubbs' catalyst provided homodimer **14** (11.3:1; *E*:*Z*). When **14** was combined with vinyl-*tetrakis*-cyclopropane **11** and exposed to Grubbs' catalyst, the cross-coupled product **15** was formed in good yield (82%)[16] with modest olefin (>5:1; *E*:*Z*) stereoselectivity. Selective removal of the benzoyl protecting group with potassium hydroxide provided polycyclopropane **16** (86% ee), which was identical to an intermediate in Barrett's total synthesis[5c] of (–)-FR-900848 (**1**).[18]



Scheme 3. (a) BzCl, Et_3N, 35%; (b) TPAP, NMO; (c) Ph_3PCH_3Br, CH_3Li, 71% for two steps; (d) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (5 mol%), 64% (11.3:1, *E*:*Z*); (e) **11**, $(Cy_3P)_2Cl_2Ru{=}CHPh$ (5 mol%), 82%; (f) KOH, CH_3OH, 89% (86% ee)

Preparation of **16** completed an enantioselective formal synthesis of (–)-FR-900848 and demonstrated the utility of olefin cross-metathesis as a tool in the synthesis of polycyclopropanated fatty acids. Although the method is limited to the formation of *E*-alkenes, olefin cross-metathesis is an attractive solution to dicyclopropyl alkene formation due to its operational simplicity and the good yields obtained in its application.

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14. Characterization data for new compounds: Compound **5**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42–7.0 (m, 10H), 5.28 (m, 2H), 1.98–1.80 (m, 2H), 1.74–1.60 (m, 2H), 1.30–1.17 (m, 2H), 1.16–1.10 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 147.5, 131.0, 128.3, 125.7, 125.6, 26.6, 25.1, 16.7. HRMS (M^+) m/z calcd for $C_{20}H_{20}$ 260.1565, found 260.1559. Compound **9**: $[\alpha]_D = -107.0$ (c 0.0242, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.49–3.35 (m, 4H), 0.90 (s, 9H), 0.90 (m, 1H), 0.89–0.78 (m, 1H), 0.77–0.63 (m, 3H), 0.62–0.48 (m, 4H), 0.31–0.17 (m, 4H), 0.15–0.03 (m, 4H), 0.05 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 67.0, 66.7, 26.0, 19.7, 19.5, 18.6, 18.4 (2), 18.1 (2), 18.0, 8.3 (3), 8.25, 0.01, −5.1. Compound **11**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.36 (ddd, 1H, J = 17.1, 10.3, 9.7 Hz), 4.99 (d, 1H, J = 17.1 Hz), 4.80 (d, 1H, J = 10.3 Hz), 3.49–3.38 (m, 2H), 1.21–1.10 (m, 1H), 0.90 (s, 9H), 0.89–0.80 (m, 1H), 0.79–0.62 (m, 3H), 0.61–0.50 (m, 5H), 0.49–0.40 (m, 2H), 0.28–0.18 (m, 2H), 0.15–0.02 (m, 2H), 0.05 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 141.9, 111.1, 66.7, 26.0, 22.3, 21.2, 19.5, 18.6, 18.4, 18.2 (2), 18.1, 11.8, 8.2, 8.1, 7.8, 0.01, −5.1. HRMS (MH^+) m/z calcd for $C_{21}H_{37}OSi$ 333.2614, found 333.2608. Compound **12**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40–7.03 (m, 5H), 5.17 (dd, 1H, J = 15.2, 7.8 Hz), 5.08 (dd, J = 15.2, 8.0 Hz), 3.55–3.35 (m, 2H), 1.98–1.68 (m, 1H), 1.66–1.54 (m, 1H), 1.21–1.00 (m, 2H), 0.90 (s, 9H), 0.95–0.31 (m, 11H), 0.30–0.18 (m, 1H), 0.18–0.02 (m, 4H), 0.05 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 132.5, 129.5, 128.3, 125.7, 125.5, 125.4, 66.7, 26.6, 26.0, 25.0, 22.0, 20.1, 19.5, 18.6, 18.4, 18.1 (2), 16.7, 11.6, 8.4, 8.2, 8.1, 7.8, −5.1. HRMS (MNH^{4+}) m/z calcd for $C_{30}H_{48}NOSi$ 466.3505, found 466.3493. Compound **13**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.15–8.00 (m, 2H), 7.61–7.52 (m, 1H), 7.50–7.41 (m, 2H), 5.45 (ddd, 1H, J = 17.1, 10.1, 8.4 Hz), 5.09 (d, 1H, J = 17.1 Hz), 4.91 (d, 1H, J = 10.1 Hz), 4.26 (dd, 1H, J = 11.5, 7.0 Hz), 4.19 (dd, 1H, J = 11.5, 7.1 Hz), 1.57–1.47 (m, 1H), 1.45–1.30 (m, 1H), 0.95–0.74 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.7, 140.1, 132.9, 130.4, 129.6, 128.3, 112.8, 68.1, 20.9, 19.3, 12.0. Compound **14**: $[\alpha]_D = -13.77$ (c 0094, CH_2Cl_2); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.13–8.00 (m, 4H), 7.62–7.51 (m, 2H), 7.50–7.40 (m, 4H), 5.18 (m, 2H), 4.29–4.20 (m, 2H), 4.18–4.12 (m, 2H), 1.46–1.38 (m, 2H), 1.33–1.23 (m, 2H), 0.85–0.63 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.7, 132.9, 131.2, 130.5, 129.6, 128.3, 68.3, 19.8, 19.1, 11.9. HRMS (MNH^+) m/z calcd for $C_{24}H_{28}NO_4$ 394.2018, found 394.2024. Compound **15**: $[\alpha]_D = -109.38$ (c 0.00256, $CDCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.12–8.01 (m, 2H), 7.60–7.51 (m, 1H), 7.50–7.41 (m, 2H), 5.1 (m, 2H), 4.34–4.21 (m, 1H), 4.19–4.08 (m, 1H), 3.52–3.38 (m, 2H), 1.67–1.53 (m, 1H), 3.52–3.38 (m, 1H), 1.35–1.20 (m, 3H), 1.10–1.01 (m, 1H), 0.98–0.66 (m, 5H), 0.89 (s, 9H), 0.65–0.48 (m, 3H), 0.43–0.32 (m, 2H), 0.30–0.05 (m, 4H), 0.04 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.7, 132.8, 132.3, 130.5, 129.6, 128.9, 128.3, 68.4, 66.7, 26.0, 21.9, 20.9, 20.0, 19.8, 19.5, 19.0, 18.6, 18.4, 18.1 (2), 11.8, 11.5, 8.2, 8.1, 7.7, 0.01, −5.1. HRMS (MNH^+) m/z calcd for $C_{32}H_{47}NO_3Si$ 507.3295, found 507.3289.
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17. Separation of diastereomers was attempted by column chromatography, although removal of all diastereomeric side products was not possible.
18. Assignment made by comparison to optical rotation and ^{1}H and ^{13}C-characterization data reported in Ref. 5c.