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Concise, diastereoconvergent synthesis of endiandric-type tetracycles by iterative cross coupling

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ABSTRACT

Both fused and bridged tetracyclic scaffolds characteristic of endiandric acid-type natural products have been prepared in just seven steps each (longest linear sequence) from Burke's commercial *cis*-2-bromovinylboronic acid MIDA ester. Three iterative Suzuki–Miyaura couplings using MIDA boronates, including the first such example of a *Z*–*Z* coupling, trigger an 8π/6π-electrocyclization cascade. The mixture of *endo* and *exo* bicycles thus formed are elaborated into tetracycles via Horner–Wadsworth–Emmons and Diels–Alder reactions. In the process, the *endo* and *exo* diastereomers interconvert to ultimately deliver the desired products.

1. Introduction

Endiandric acid derivatives are a family of natural products isolated from plants in the *Endiandra* and *Beilschmiedia* genera. Approximately half of these secondary metabolites exhibit antibiotic, anti-inflammatory, antimalarial, antitubercular, or cytotoxic activity.[1] The vast majority of endiandric acid derivatives possess characteristic fused (**1**,[2] Fig. 1) or bridged (**2** and **3**[3]) tetracyclic cores, and most are optically inactive despite harboring multiple stereogenic centers. This observation led Black, Banfield, and coworkers to propose that endiandric acid tetracycles naturally arise from non-enzymatic cyclizations of achiral polyene precursors.[4] Black and Banfield's pericyclic cascade hypothesis found support in Nicolaou's syntheses of endiandric acids A-G,[5–8], which established (*E*,*Z*,*Z*,*E*)-tetraenes as viable biosynthetic precursors for this family of natural products. More recently, Sherburn and coworkers demonstrated that (*Z*,*Z*,*Z*,*Z*)-tetraenes can also undergo the pericyclic cascade to produce endiandric acids, though only at elevated temperatures.[9–11]

The impressive biomimetic syntheses by Nicolaou and Sherburn relied upon *cis*-selective reductions of conjugated alkynes (diynes or tetraynes) to generate octatetraene intermediates and trigger 8π/6π electrocyclization cascades. We sought to develop a concise and modular approach to endiandric acid derivatives with both fused and bridged tetracycles by exploring an alternate route to the 8π/6π electrocyclization cascade. We were particularly interested in prompting these electrocyclizations through a palladium-mediated *Z*–*Z* coupling of two (*Z*,*E*)-diene fragments[12,13] rather than partial reduction of alkynes.

We anticipated that Burke's iterative cross-coupling (ICC) method would enable facile assembly of an (*E*,*Z*,*Z*,*E*)-tetraene from smaller alkenyl building blocks using Suzuki–Miyaura coupling reactions. Our overall retrosynthetic approach to exemplary fused (**4**) and bridged (**5**) tetracycles is shown in Scheme 1. We envisioned that both tetracycles could be synthesized from a common bicyclic

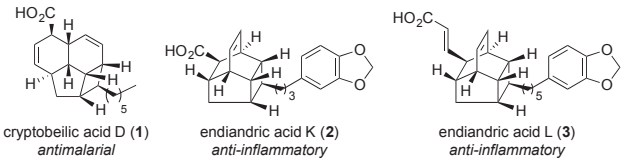

Fig. 1. Representative bioactive endiandric acid derivatives with fused or bridged tetracyclic cores.[2,3]

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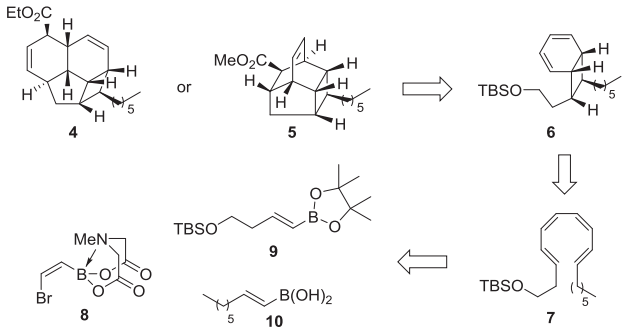
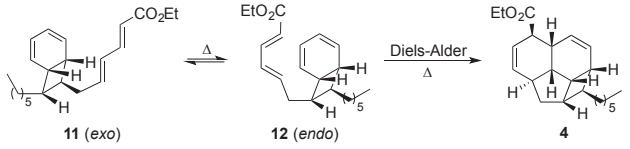
intermediate **6** obtained from the 8π/6π electrocyclization cascade of tetraene **7**, which may be prepared from commercially-available alkenyl building blocks **8**–**10** using ICC.



Scheme 1. Retrosynthetic analysis for fused and bridged tetracycles.

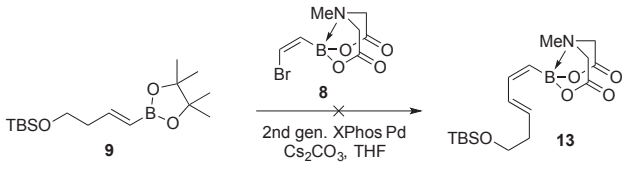
An additional feature of our synthetic plan is its reliance on the thermal interconversion of diastereomeric *exo* and *endo* bicycles (Scheme 2). We anticipated that the electrocyclization cascade would result in roughly equal amounts of *exo* and *endo* products, yet the tetracycle-generating intramolecular Diels–Alder reactions are only possible with *endo* compounds (e.g., **12**). We therefore hoped that the *exo*/*endo* equilibration observed by Nicolaou and co-workers upon heating endiandric acids D-G[8,14] would also enable conversion of *exo* diastereomer **11** to tetracycle **4** via *endo* dienoate **12**, rendering our synthesis diastereoconvergent.



Scheme 2. Thermally equilibrating *exo* and *endo* bicycles should converge on a single tetracycle.

2. Results and discussion

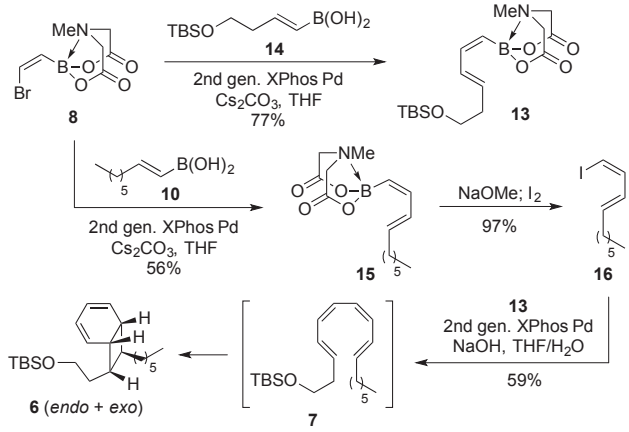
Burke recently described a general procedure for the Suzuki coupling of vinyl pinacol boronates and vinyl halides in the presence of MIDA boronates.[15] However, our attempts to synthesize dienyl MIDA boronate **13** from *cis*-2-bromovinyl-boronic acid MIDA ester (**8**)[16] and pinacol boronate **9** were unsuccessful (Scheme 3),



Scheme 3. Unsuccessful *Z*,*E* coupling with (*Z*)-bromo MIDA boronate **8** and pinacol boronate **9**.

even though **9** coupled smoothly with the corresponding *trans*-2-bromovinyl-boronic acid MIDA ester.

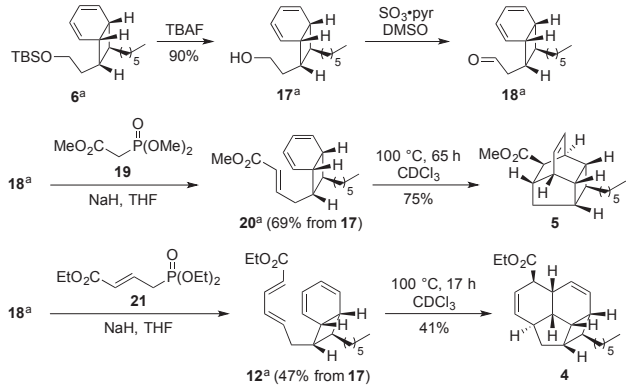
Indeed, **8** has not yet been reported to undergo Suzuki–Miyaura cross-couplings with pinacol boronates; only (less sterically hindered) boronic acids have been utilized as coupling partners.[15,16] We therefore hydrolyzed pinacol boronate **9** to the boronic acid as reported by Mehta[17] and were gratified to see that boronic acid **14** successfully underwent coupling with **8** to afford (*Z*,*E*)-dienyl MIDA boronate **13** (Scheme 4). Boronic acid **10** was coupled with **8** in a similar fashion to give dienyl MIDA boronate **15**. Purification of both MIDA boronate products was trivial using Burke's silica filtration method,[18] washing the crude product with 1.5% MeOH in Et_2O and eluting with acetone or THF.



Scheme 4. Iterative cross couplings provide bicycle **6**.

Direct conversion of MIDA boronate **15** to iodide **16** was accomplished with complete retention of configuration in high yield by treatment with sodium methoxide followed by I_2.[19] Once generated, the iodide was used immediately in the subsequent coupling step. We were delighted to observe the formation of bicycle **6** (as an inseparable mixture of *endo* and *exo* diastereomers) directly from MIDA boronate **13** and iodide **16** under Burke's in situ deprotection/coupling conditions.[15,19] The yield of this reaction improved notably when performed in a subdued light environment, as **16** is light-sensitive.

From bicycle **6**, desilylation and Parikh–Doering oxidation yielded bicyclic aldehyde **18** (Scheme 5). Horner–Wadsworth–Emmons reactions of **18** resulted in enoate **20** and dienoate **12**, still as *endo*/*exo* mixtures. In each case, as we predicted, heating converted both diastereomers of **20** and **12** to the desired Diels–Alder products: bridged tetracycle **5** and fused tetracycle **4** (cryptobeilic acid D ethyl ester), respectively.



Scheme 5. Diastereoconvergent Diels–Alder reactions provide fused and bridged tetracycles ([a] *endo*/*exo* mixture).

We note that in the conversion of tethered dienoate **12** to fused tetracycle **4**, a small amount of bridged product was detected in the crude ^{1}H NMR (ca. 12:1 fused/bridged), with a characteristic enoate signal at 6.77 ppm (dd, J=15.7, 8.2 Hz) that closely matches those of endiandric acid L (**3**) and related structures.[3,20,21] Thus the tethered diene may act as a dienophile to some extent, but the preferred mode of reactivity is as a diene to provide the fused tetracycle.[22] Indeed, vastly more endiandric-type tetracycles have been isolated with fused skeletons (49) compared to their bridged isomers from this alternate Diels–Alder mode (3).[1] Further, all three of these bridged enoate metabolites are racemic in nature, and their fused analogs are known, strongly suggesting that enzymes do not mediate the Diels–Alder regioselectivity. Further studies on competitive biomimetic Diels–Alder reactions to give fused or bridged tetracycles are ongoing and will be reported in due course.

3. Conclusions

In summary, we have described a concise route to both fused and bridged endiandric-type tetracycles using an iterative Suzuki–Miyaura strategy. In each case, the longest linear sequence is seven steps from commercial MIDA boronate **8**. This approach is likely applicable to both natural and unnatural compounds of this structural type.

4. Experimental section

Commercial reagents were purchased from Sigma–Aldrich, TCI America, or Spectrum and used without further purification. Anhydrous DMSO was purchased from Sigma–Aldrich. Reagent-grade acetone was purchased from Spectrum. Anhydrous CH_2Cl_2, THF, and toluene were obtained from a SolvPure solvent purification system. Triethylamine was distilled over CaH_2 and stored over KOH pellets.

Unless otherwise noted, all reactions were performed in flame-dried glassware under positive argon pressure at room temperature. Reactions were monitored by TLC on 0.250 mm Sorbent Technologies glass-backed silica gel plates and visualized under UV light (254 nm) or by staining with $KMnO_4$ or an acidic solution of *p*-anisaldehyde followed by brief heating on a hot plate. NMR spectra were recorded on a Bruker Avance 400 MHz instrument at ambient temperature in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the residual solvent signals (^{1}H, 7.26; ^{13}C, 77.0).

4.1. ((1*Z*,3*E*)-6-((*tert*-Butyldimethylsilyl)oxy)hexa-1,3-dien-1-yl) MIDA boronate (13)

A mixture of crude boronic acid **14** (101.65 mg, 0.434 mmol),[17] *cis*-2-bromovinylboronic acid MIDA ester (114.8, 0.439 mmol), Cs_2CO_3 (426.7 mg, 1.31 mmol) and XPhos Pd G2 (34.1 mg, 0.043 mmol) was evacuated and then placed under a nitrogen atmosphere. THF (2.5 mL) was added and the mixture was stirred for 22 h. The reaction mixture was diluted in acetone (20 mL) and Cs_2CO_3 was removed by vacuum filtration. The filtrate was concentrated in vacuo, dissolved in CH_2Cl_2, loaded onto a Celite/silica plug and purified by washing with hexanes, then 1.5% MeOH/Et_2O, then eluting with acetone. Concentration in vacuo afforded **13** as a white crystalline solid (124.1 mg, 77% yield). R_f (EtOAc) 0.39; IR (thin film) 2927, 1770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (dd, J=13, 12 Hz, 1H), 6.57 (dd, J=15, 12 Hz, 1H), 5.81 (dt, J=15, 7.5 Hz, 1H), 5.15 (d, J=14 Hz, 1H), 3.83 (d, J=16 Hz, 2H), 3.68 (d, J=16 Hz, 2H), 3.65 (t, J=6.6 Hz, 2H), 2.86 (s, 3H), 2.34 (dt, J=7.5, 6.6 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 145.8, 136.1, 130.2, 62.7, 61.6, 46.9, 36.4, 25.9, 18.3, -5.2; HRMS (ESI): $[M+H]^+$ found 368.2071, calculated 368.2059.

4.2. ((1*Z*,3*E*)-Deca-1,3-dien-1-yl) MIDA boronate (15)

A mixture of boronic acid **10** (300 mg, 1.91 mmol), *cis*-2-bromovinylboronic acid MIDA ester (400 mg, 1.53 mmol), Cs_2CO_3 (1.52 g, 4.58 mmol) and XPhos Pd G2 (120 mg, 0.15 mmol) was evacuated and then placed under a nitrogen atmosphere. THF (5 mL) was added and the mixture was stirred for 24 h. The reaction mixture was diluted in acetone (20 mL) and Cs_2CO_3 was removed by vacuum filtration. The filtrate was concentrated in vacuo, dissolved in CH_2Cl_2, loaded onto a Celite/silica plug and purified by washing with hexanes, then 1.5% MeOH/Et_2O, then eluting with acetone. Concentration in vacuo afforded **15** as a yellow wax (250 mg, 56% yield). R_f (EtOAc) 0.5; IR (thin film) 2924, 1761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (dd, J=13, 12 Hz, 1H), 6.48 (dd, J=12, 7.3 Hz, 1H), 5.78 (dt, J=15, 7.3 Hz, 1H), 5.12 (d, J=14 Hz, 1H), 3.99 (d, J=16 Hz, 2H), 3.70 (d, J=17 Hz, 2H), 2.85 (s, 3H), 2.09 (dt, J=7.1, 7.0 Hz, 2H), 1.35 (m, 2H), 1.28 (m, 6H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 146.3, 140.3, 128.5, 61.6, 46.8, 32.8, 31.7, 29.2, 28.9, 28.9, 22.6, 14.1; HRMS (ESI): $[M+H]^+$ found 294.1867, calculated 294.1871.

4.3. (1*Z*,3*E*)-1-Iododeca-1,3-diene (16)

A mixture of MIDA boronate **15** (113 mg, 0.38 mmol), and NaOMe (0.5 M in MeOH, 2.3 mL, 1.2 mmol) in THF (2 mL) was stirred for 15 min, changing color from clear orange to cloudy yellow. The reaction mixture was placed in a subdued light environment and I_2 (1.0 M in THF, 760 μL, 0.76 mmol) was added. The reaction mixture was stirred for 10 min. The reaction mixture was diluted in saturated $Na_2S_2O_3$ (20 mL) and hexanes (20 mL) and transferred to a separatory funnel. The layers were separated, and the organic layer was washed with saturated $Na_2S_2O_3$ (2×10 mL). The organic layer was concentrated in vacuo to afford **16** as a red oil (99 mg, 97% yield), which was used immediately in the cross-coupling reaction. R_f (hexanes) 0.98; IR (thin film) 2926 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (dd, J=9.7, 7.6 Hz, 1H), 6.21 (ddq, J=15, 9.8, 1.4 Hz, 1H), 6.08 (dq, J=7.6, 1.4 Hz, 1H), 6.00 (dt, J=15, 7.6 Hz, 1H), 2.13 (q, J=6.9 Hz, 2H), 1.41 (m, 2H), 1.29 (m, 6H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 138.5, 130.3, 79.2, 33.0, 31.7, 28.9, 28.9, 22.6, 14.1; HRMS (ESI): $[M+H]^+$ found 264.0363, calculated 264.0370.

4.4. *tert*-Butyl(2-(8-hexylbicyclo[4.2.0]octa-2,4-dien-7-yl)ethoxy)dimethylsilane (6, *endo*/*exo* mixture)

A mixture of MIDA boronate **14** (0.1776 g, 0.484 mmol), iododiene **16** (0.1121 g, 0.424 mmol) and XPhos Pd G2 (17.8 mg, 0.02 mmol) was evacuated and refilled with a nitrogen atmosphere three times in a light-reduced environment. THF (4 mL) and aq NaOH (4 M, 0.3 mL, 1.2 mmol) were added. The solution was bubbled through with argon and stirred for 48 h. The reaction mixture was diluted in hexanes (40 mL) and H_2O (20 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with hexanes (2×40 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL) and dried over $MgSO_4$. The filtrate was concentrated in vacuo and purified via flash chromatography (hexanes/toluene 100:0 → 90:10) to afford the title compound **6** (87 mg, 59% yield) as a clear oil. R_f (hexanes/toluene 9:1) 0.24; IR (thin film) 2954, 2926 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ 5.84 (m, 1H), 5.60 (m, 3H), 3.54 (dt, J=1.5, 2.7 Hz, 2H), 3.10 (m, 1H), 2.45 (m, 2H), 2.29 (m, 1H), 1.65–1.91 (m, 2H), 1.25 (m, 10H), 0.89 (s, 9H), 0.88 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.7, 127.3, 127.1, 127.1, 124.0, 121.5, 121.3, 62.5, 62.3, 52.4, 51.5, 49.2, 48.2, 39.8, 37.4, 37.1, 36.6, 34.5, 34.2, 33.8, 32.0, 32.0, 31.1, 30.6, 29.8, 29.7, 29.6, 28.3, 28.2, 26.1, 22.8, 22.8, 18.5, 18.5, 14.3; HRMS (ESI): $[M+H]^+$ found 349.2933, calculated 349.2927.

4.5. 2-(8-Hexylbicyclo[4.2.0]octa-2,4-dien-7-yl)ethan-1-ol (17, *endo*/*exo* mixture)

A solution of bicyclic silyl ether **6** (38.4 mg, 0.110 mmol) and TBAF (1.0 M in THF, 250 μL, 0.25 mmol) in THF (4 mL) was stirred for 1.5 h. The reaction mixture was diluted in H_2O (10 mL) and Et_2O (10 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The filtrate was concentrated in vacuo and purified by flash chromatography (hexanes/EtOAc 100:0→50:50) to afford **17** as a clear oil (23.3 mg, 90% yield). R_f (hexanes/EtOAc 3:1) 0.65; IR 3331, 2921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (m, 1H), 5.55–5.69 (m, 3H), 3.56–3.64 (m, 2H), 3.12 (m, 1H), 2.27–2.53 (m, 3H), 1.73–1.96 (m, 2H), 1.41–1.68 (m, 1H), 1.25 (m, 10H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.7, 127.3, 126.8, 126.6, 124.3, 124.1, 121.3, 62.1, 62.0, 52.4, 51.6, 48.8, 47.6, 39.3, 37.3, 37.1, 36.6, 34.7, 34.0, 33.9, 32.0, 32.0, 30.6, 29.8, 29.7, 29.6, 28.3, 28.3, 22.8, 22.8, 14.3; HRMS (ESI): $[M+H]^+$ found 235.2058, calculated 235.2056.

4.6. 2-(8-Hexylbicyclo[4.2.0]octa-2,4-dien-7-yl)ethanal (18, *endo*/*exo* mixture)

A solution of bicyclic alcohol **17** (13.8 mg, 0.059 mmol) and Et_3N (46 μL, 0.33 mmol) dissolved in CH_2Cl_2 (0.8 mL) was cooled to 0 °C. In a separate vial, SO_3·pyr (31.4 mg, 0.197 mmol) was dissolved in DMSO (0.2 mL) and stirred for 3 min. The SO_3·pyr/DMSO solution was added dropwise to the reaction mixture and stirred for 70 min. EtOAc (10 mL) and H_2O (10 mL) were added to the reaction and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The filtrate was concentrated in vacuo to afford crude **18** (14.7 mg) as a clear liquid, which was carried on to the next step without further purification. R_f (hexanes/EtOAc 3:1) 0.71; IR 2922, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (t, J=3.7 Hz, 1H), 9.69 (t, J=6 Hz, 0.8H), 5.85–5.91 (m, 2.7H), 5.57–5.74 (m, 7.7H), 5.42 (dd, J=24.8, 10.4 Hz, 1.2H), 3.12–3.26 (m, 2.8H), 2.78–2.87 (m, 2.7H), 2.45–2.71 (m, 9.4H), 2.24-2.35 (m, 1.7H), 1.38–1.65 (m, 8.2H), 1.26 (m, 39.3H), 0.86–0.89 (m, 16.5H); HRMS (ESI): $[M+H]^+$ found 233.1902, calculated 233.1900. **Reported as a mixture of endo and exo products, calibrated to the larger aldehydic peak.*

4.7. Bicyclic methyl enoate 20 (*endo*/*exo* mixture)

To a solution of trimethyl phosphonoacetate (160 μL) in THF (0.5 mL) was added NaH (60% dispersion in mineral oil, 24.1 mg, 1 mmol), resulting in a milky white solution. In a separate vial, crude bicyclic aldehyde **18** (5.9 mg, 0.025 mmol) was dissolved in THF (0.5 mL), and a portion of the prepared sodium salt of the trimethyl phosphonoacetate solution (40 μL, 0.079 mmol) was added. The mixture was stirred for 19.5 h and diluted with 50% $NaHCO_3$ (1 mL). The mixture was transferred to a separatory funnel containing hexanes (3 mL), and the layers were separated. The aqueous layer was extracted with hexanes (2×3 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc 100:0→80:20) to afford **20** as a clear oil (4.7 mg, 69% two-step yield from **17**). R_f (hexanes/EtOAc 4:1) 0.53; IR 2922, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.85–6.97 (m, 1H), 5.78–5.87 (m, 3H), 5.48–5.67 (m, 5H), 3.71 (s, 3H), 3.14 (m, 1H), 2.50 (m, 2H), 1.24 (m, 10H), 0.87 (t, J=6.9 Hz, 3H).

4.8. Bridged tetracyclic methyl ester 5

A solution of bicyclic methyl enoate **20** (5.6 mg, 0.024 mmol) in $CDCl_3$ (0.6 mL) in a J. Young NMR tube was heated in an oil bath at 70 °C for 96 h and 100 °C for 65 h. Reaction progress was monitored by ^1H NMR. After the starting material had been consumed, the reaction was filtered through a silica column (hexanes/EtOAc 100:0→98:2) to yield **5** as a colorless film (4.2 mg, 75% yield). R_f (hexanes) 0.23; IR 2920, 1739 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): δ 6.19 (m, 2H), 3.63 (m, 3H), 3.00 (m, 1H), 2.82 (m, 1H), 2.67 (m, 1H), 2.58 (m, 1H), 2.34 (m, 1H), 2.22 (m, 1H), 1.90 (m, 1H), 1.63 (m, 1H), 1.51–1.56 (m, 1H), 1.48 (m, 1H), 1.26 (m, 10H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 175.5, 131.9, 131.4, 51.8, 49.2, 42.1, 40.4, 40.3, 39.7, 39.6, 38.6, 36.5, 35.3, 32.1, 29.9, 29.5, 27.4, 22.8, 14.3; HRMS (ESI) $[M+H]^+$ found 289.2154, calculated 289.2162.

4.9. Bicyclic ethyl dienoate 12 (*endo*/*exo* mixture)

To a suspension of NaH (60% dispersion in mineral oil, 14.4 mg, 0.597 mmol) in THF (1 mL) was added triethyl-3-phosphonocrotonate (150 μL), resulting in a dark orange solution. In a separate vial, crude bicyclic aldehyde **18** (9.9 mg, 0.042 mmol) was dissolved in THF (1 mL), and the prepared sodium salt of the triethyl 3-phosphonocrotonate solution (150 μL, 0.296 mmol) was added. The mixture was stirred for 2.5 h and stored in the freezer over the weekend. The reaction mixture was warmed to room temperature and diluted with H_2O (5 mL) and satd $NaHCO_3$ (5 mL). The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with EtOAc (10 mL). The organic layer was washed with $NaHCO_3$ (1:1 water/satd $NaHCO_3$, 10 mL), brine (10 mL), and dried over $MgSO_4$. The filtrate was concentrated in vacuo and purified by flash chromatography (hexanes/EtOAc 100:0→98:2) to afford **12** as a clear oil (6.1 mg, 47% two-step yield from **17**). R_f (hexanes/EtOAc 19:1) 0.39; IR 2917, 1717 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 6.00–6.21 (m, 2H), 5.76–5.90 (m, 2H), 5.50–5.67 (m, 4H), 4.17–4.22 (q, J=7.1 Hz, 2H), 3.14 (m, 1H), 2.31–2.53 (m, 5H), 1.29 (t, J=7.1 Hz, 3H), 1.25 (m, 10H), 0.87 (t, J=6.9 Hz, 3H).

4.10. Cryptobeilic acid D ethyl ester (4)

A solution of bicyclic ethyl dienoate **12** (6.1 mg, 0.019 mmol) in $CDCl_3$ (0.5 mL) in a J. Young NMR tube was heated in an oil bath at 100 °C for 17 h. Reaction progress was monitored by ^1H NMR. After the starting material had been consumed, the reaction was filtered through a silica column (hexanes/EtOAc 100:0 → 98:2) to yield **4** as a colorless film (2.5 mg, 41% yield, 12:1 ratio of fused/bridged isomers). R_f (hexanes/EtOAc 19:1) 0.67; IR 2922, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.19 (m, 1H), 5.71 (m, 1H), 5.64 (m, 1H), 5.45 (m, 1H), 4.16 (q, J=7.0 Hz, 2H), 2.97 (m, 1H), 2.95 (m, 1H), 2.64 (m, 1H), 2.55 (m, 1H), 2.26 (m, 1H), 2.24 (m, 1H), 1.73 (m, 2H), 1.57 (m, 1H), 1.46 (m, 1H), 1.33 (m, 1H), 1.27 (m, 13H), 0.88 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 134.1, 129.9, 129.3, 124.6, 60.8, 49.6, 46.0, 42.1, 41.2, 37.2, 36.9, 35.0, 34.8, 33.1, 32.8, 31.9, 29.7, 27.0, 22.6, 14.2, 14.1; HRMS (ESI) $[M+H]^+$ found 329.2474, calculated 329.2481.

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Supplementary data

Supplementary data (Characterization data for selected compounds are available) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.02.040.

References and notes

1. Lenta, B. N.; Chouna, J. R.; Nkeng-Efouet, P. A.; Sewald, N. *Biomolecules* **2015**, *5*, 910–942.
2. Talontsi, F. M.; Lamshöft, M.; Bauer, J. O.; Razakarivony, A. A.; Andriamihaja, B.; Strohmann, C.; Spiteller, M. *J. Nat. Prod.* **2013**, *76*, 97–102.
3. Huang, Y.-T.; Chang, H.-S.; Wang, G.-J.; Cheng, M.-J.; Chen, C.-H.; Yang, Y.-J.; Chen, I.-S. *J. Nat. Prod.* **2011**, *74*, 1875–1880.
4. Bandaranayake, W. M.; Banfield, J. E.; Black, D. S. C. *J. Chem. Soc., Chem. Commun.* **1980**, 902–903.
5. Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555–5557.
6. Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5557–5558.
7. Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558–5560.
8. Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560–5562.
9. Drew, S. L.; Lawrence, A. L.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 4221–4224.
10. Drew, S. L.; Lawrence, A. L.; Sherburn, M. S. *Chem. Sci.* **2015**, *6*, 3886–3890.
11. Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130–7131.
12. Lim, H. N.; Parker, K. A. *Org. Lett.* **2013**, *15*, 398–401.
13. Beaudry, C. M.; Trauner, D. *Org. Lett.* **2005**, *7*, 4475–4477.
14. Nicolaou, K. C.; Petasis, N. A. In *Strategies and Tactics in Organic Chemistry*; Lindberg, T., Ed.; Academic: San Diego, 1984; pp 155–173.
15. Woerly, E. M.; Roy, J.; Burke, M. D. *Nat. Chem.* **2014**, *6*, 484–491.
16. Woerly, E. M.; Struble, J. R.; Palyam, N.; O'Hara, S. P.; Burke, M. D. *Tetrahedron* **2011**, *67*, 4333–4343.
17. Vasamsetty, L.; Khan, F. A.; Mehta, G. *Tetrahedron* **2015**, *71*, 3209–3215.
18. Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. *Science* **2015**, *347*, 1221–1226.
19. Fujii, S.; Chang, S. Y.; Burke, M. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7862–7864.
20. Apel, C.; Gény, C.; Dumontet, V.; Birlirakis, N.; Roussi, F.; Pham, V. C.; Doan Thi Mai, H.; Nguyen, V. H.; Chau, V. M.; Litaudon, M. *J. Nat. Prod.* **2014**, *77*, 1430–1437.
21. Azmi, M. N.; Gény, C.; Leverrier, A.; Litaudon, M.; Dumontet, V.; Birlirakis, N.; Guéritte, F.; Leong, K. H.; Halim, S. N. A.; Mohamad, K.; Awang, K. *Molecules* **2014**, *19*, 1732–1747.
22. In Nicolaou's synthesis of endiandric acids A and B, the tethered phenyldiene reacted exclusively as a diene to give the fused product. No bridged product was observed (see Ref. 3).