Tetrahedron: *Asymmetry* xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Diastereoselective synthesis of a highly functionalized cyclohexene embedded with a quaternary stereogenic centre by self Diels–Alder dimerization of a [3]dendralene attached to a (−)-menthol auxiliary

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ARTICLE INFO

Article history:
Received 22 August 2013
Accepted 7 November 2013
Available online xxxx

ABSTRACT

A novel route to a chiral functionalized [3]dendralene attached to a (−)-menthol auxiliary has been developed, which involves a dimethylsulfonium methylide mediated olefination of a substituted ethenylidene phosphonoacetate (−)-menthyl ester, followed by a Horner–Wordsworth–Emmons reaction with 4-bromobenzaldehyde. The chiral [3]dendralene was reactive enough to undergo intermolecular Diels–Alder cyclodimerization to give the highly substituted cyclohexene with very high regio- and diastereoselectivity.

1. Introduction

Although chiral cyclohexenes have been used as intermediates in organic synthesis,[1–4] they are not very common structural units in medicinal chemistry. This is probably due to the poor availability of suitable synthetic methods that provide chiral substituted cyclohexenes with high enantiomeric excess and in large quantities. In contrast, the cyclohexene ring is common in natural products such as steroids, terpenes, alkaloids, vitamin A and taxol. The synthesis of highly functionalized cyclohexene with multiple stereocentres and having quaternary chiral centre[5] is a challenging task. Recently, a highly functionalized cyclohexene with a quaternary centre has been found in the dimeric triterpenoid dibelamcandel A (Fig. 1) wherein the six-membered ring links two iridal type triterpenoid nuclei.[6] It has been proposed[6] that the natural product is probably formed by a highly regio- and stereoselective Diels–Alder cyclodimerization of an iridal triterpenoid (Fig. 1) with a linear conjugated triene feature.

Compared to linear conjugated systems, cross-conjugated molecules contain three unsaturated groups in which two of them are conjugated to a third unsaturated centre, but not conjugated to each other. One such class of molecules is that of the [3]dendralenes[7] (Fig. 2, $n = 1$), which have remained relatively unexplored, probably due to limited preparation methods[8–17] especially for substituted systems[18–21] and together with an unusual reactivity pattern.[22–24]

Recently we developed[25] a method for the synthesis of [3]dendralenes substituted at multiple positions based on a

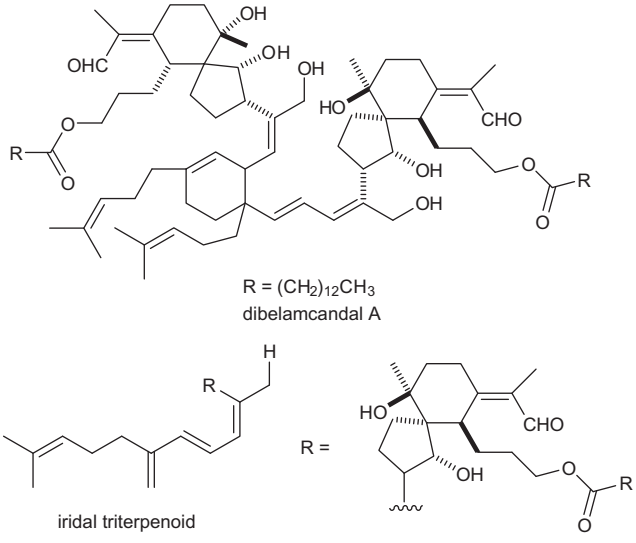

Figure 1. Dimeric triterpenoid dibelamcandel A and its biosynthetic precursor iridal triterpenoid.

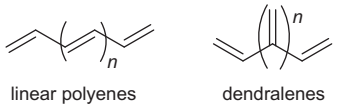

Figure 2. Structural features of linear polyenes and dendralenes.

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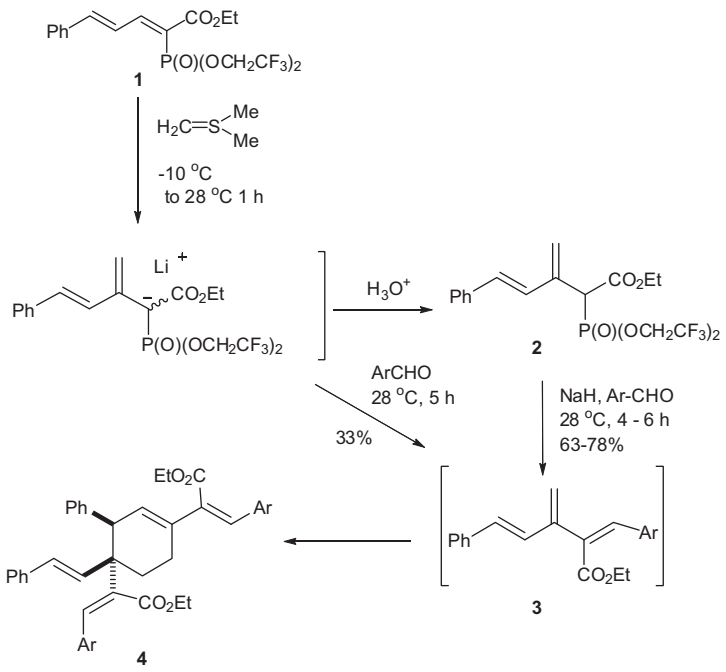
http://dx.doi.org/10.1016/j.tetasy.2013.11.005



Scheme 1. Synthesis of functionalized [3]dendralenes and their Diels–Alder cyclodimerization.[25]

dimethylsulfonium methylide[26] mediated sequential tandem double olefination[27–30] of suitably substituted 1,3-dienyl phosphonate **1** and aldehydes (Scheme 1). The reaction took place via 1,3-butadien-2-ylphosphonoacetate **2**. The desired [3]dendralenes **3** were formed as reactive intermediates, which could only be monitored during the reaction but not isolated. Under the reaction conditions, they underwent an in situ Diels–Alder cyclodimerization to give highly functionalized cyclohexene products **4** embedded with a quaternary centre. The overall process proceeded with moderate to good yield but with excellent regio- and stereoselectivity. This prompted us to investigate the possibility of an asymmetric induction strategy for making such cyclohexenes. Herein we report a novel route to a chiral functionalized [3]dendralene attached to a (−)-menthol auxiliary and its self Diels–Alder cyclodimerization to give a highly substituted cyclohexene embedded with a quaternary stereogenic centre with high regio- and diastereoselectivity.

2. Results and discussion

For the synthesis of chiral [3]dendralenes,[31] (−)-menthol was chosen as the chiral auxiliary. At first, (−)-menthyl bromoacetate **5** upon Arbuzov reaction with triethylphosphite gave the ester of diethylphosphonoacetate **6**, which was then treated with phosphorus pentachloride followed by 2,2,2-trifluoroethanol to give the menthyl ester of bis-(2,2,2-trifluroethyl)phosphonoacetate **7** (Scheme 2). Knoevenagel condensation of phosphonoacetate **7** with cinnamaldehyde in the presence of piperidinium benzoate provided the desired 2-phenylethenylidene phosphonoacetate **8** in 78% yield (Scheme 2) as a mixture of the (2*E*,4*E*)- and (2*Z*,4*E*)-isomers in a ratio of 7:3. This mixture of phosphonoacetates was added to dimethylsulfonium methylide (generated from trimethylsulfonium iodide and *n*-butyl lithium in THF) and then quenched with water to give the 1,3-butadien-2-ylphosphonoacetate **9** in 64% yield as an inseparable 1:1 mixture of diastereoisomers. This mixture of phosphonates **9** was then mixed with 1 equiv of 4-bromobenzaldehyde and treated with NaH in THF which resulted in the formation of two diastereoisomeric Diels–Alder homodimerisation products **11** and **12** in a ratio of 8:2 (Scheme 2) in 52% overall yield from dienic phosphonoacetates **9**. The diastereoisomeric Diels–Alder homodimerisation products should have formed via the intermediate [3]dendralene **10**. The diastereoisomers (−)-**11** and (+)-**12** were separated and the structure of the major diastereoisomer (−)-**11** was confirmed by spectroscopic data and by X-ray crystallography[32,33] (Fig. 3).

The regio- and stereoselectivity of this Diels–Alder reaction was very distinctive in the sense that the 3-methylene group of the [3]dendralenes **10** participated exclusively as the dienophile component. Furthermore, this 3-methylene group and the double bond at the 4-position of the [3]dendralene **10** acted together as the diene component in the Diels–Alder reaction. The orientation of the diene component and the dienophile component are such that bonding took place between the unsubstituted carbons of the 3-methylene groups (from both the diene and dienophile, both) and two substituted carbons, at the 3-position (dienophile) and the 5-position (diene) leading to only one regio-isomer with the generation of a quaternary stereogenic centre in **11/12**. The diastereoselectivity was controlled by the chirality present in the (−)-menthol auxiliary.

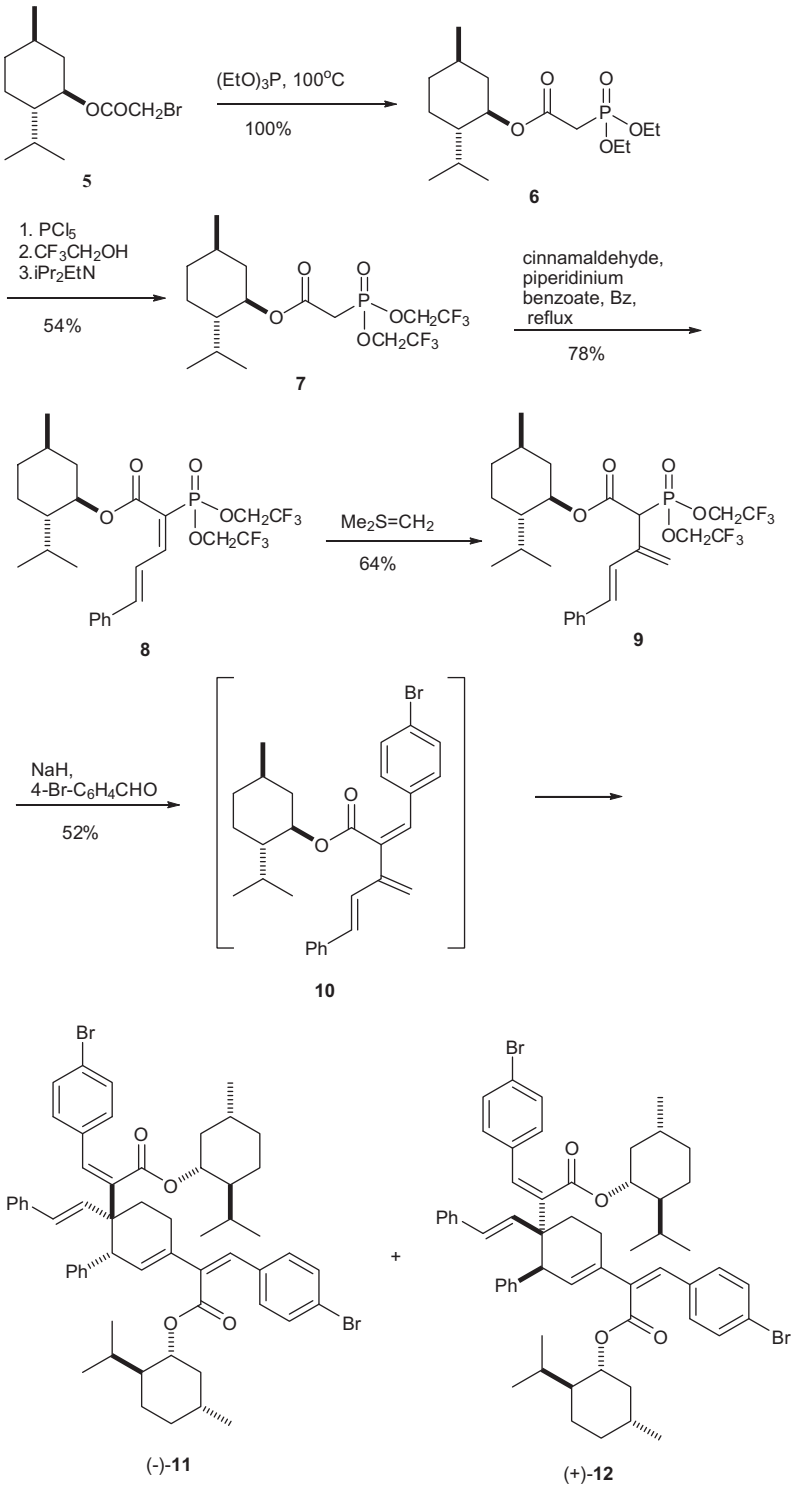
3. Conclusion

In conclusion, a route to a densely functionalized chiral [3]dendralene has been reported on using a (−)-menthol auxiliary and dimethylsulfonium methylide as the olefination agent. The chiral [3]dendralene could not be isolated but was reactive enough to undergo intermolecular Diels–Alder cyclodimerization to give a highly substituted cyclohexene with very high regio- and diastereoselectivity. The present methodology, thus holds promise to synthesize densely functionalized complex chiral cyclohexenes with a quaternary centre similar to dibelamcandel A.

4. Experimental

4.1. General

All reactions were performed in oven-dried (120 °C) or flame-dried glass apparatus under dry N_2 or argon atmosphere.



Scheme 2. Synthesis of a functionalized chiral [3]dendralene and its Diels–Alder cyclodimerization.

Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone. *n*-BuLi (1.6 M in hexane) was purchased from Aldrich. (−)-Menthol, 2,2,2-trifluoroethanol and 4-bromobenzaldehyde were purchased from Aldrich. Solvent removal was carried out using a rotary evaporator connected to a dry ice condenser. TLC (0.5 mm) was carried out using homemade silica plates with a fluorescence indicator. Column chromatography was performed on silica gel (230–400 mesh). The ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker 200/700 MHz spectrometers. The spectra were referenced to residual chloroform (δ 7.25 ppm, ^{1}H; δ 77.00 ppm, ^{13}C). The IR spectra were recorded with a JASCO FT IR spectrophotometer in NaCl cells or in KBr discs. Peaks are reported in cm^{-1}. Melting points (mp) were determined on a Fischer John's melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 polarimeter. Elemental analyses (C, H, N) were carried out at Bio-Organic Division BARC, Mumbai, India.

Suitable X-ray quality crystals of (−)-**11** were grown in hexanes–EtOAc and X-ray diffraction studies were undertaken. X-ray crystallographic data were collected from single crystal samples

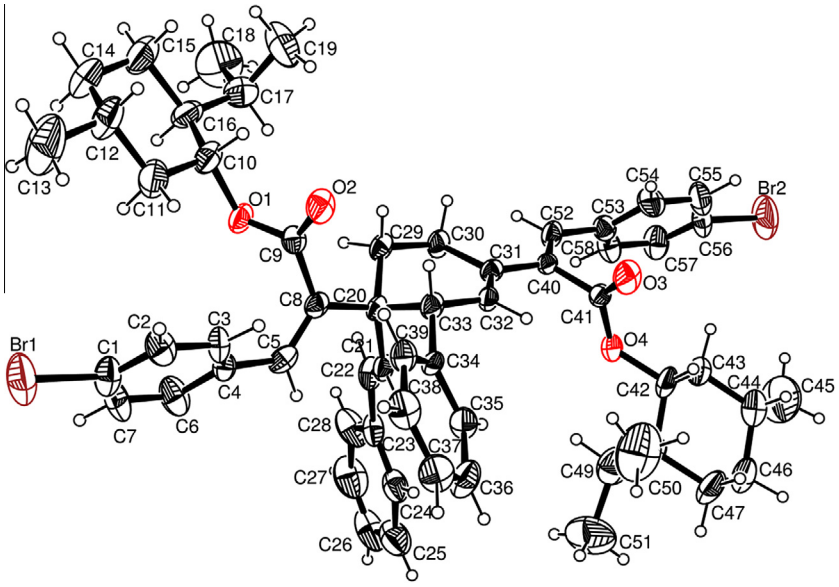


Figure 3. ORTEP diagram of (−)-**11**.

of volume 0.23 × 0.18 × 0.13 mm^3 at 150(2) K mounted on a OXFORD DIFFRACTION XCALIBUR-S CCD system equipped with graphite monochromated Mo Kα radiation (0.71073 Å). The data were collected by ω-2θ scan mode, and absorption correction was applied by using multi-Scan. The structure was solved by direct methods SHELX-97 and refined by full-matrix least squares against F^2 using SHELX-97[34] software. Non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were geometrically fixed and allowed to refine using a riding model.

4.2. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate 5

A solution of (−)-menthol (3 g, 19 mmol) and pyridine (1.54 mL, 19 mmol) in dichloromethane (30 mL) was cannulated slowly to a solution of bromoacetyl bromide (1.67 mL, 19 mmol) in dichloromethane (20 mL) at −78 °C. After stirring for 10 min, the reaction mixture was allowed to return to room temperature. The reaction mixture was then poured into water and extracted with dichloromethane. The organic extract was concentrated and the residue was purified by column chromatography to provide bromoacetate **5** (5.25 g, 100%) as a colourless liquid. R_f = 0.71 (hexane–EtOAc, 95:5); $[\alpha]_D^{24} = -64.8$ (*c* 4.08, MeOH); IR (film): 2956, 2928, 2870, 1731, 1456, 1422, 1387, 1370, 1278, 1168, 1178, 1009, 983, 921, 843 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.77 (1H, dt, *J* = 10.9, 4.4 Hz, OCH), 3.85 (2H, s, $BrCH_2$), 2.15–1.87 (2H, m, CH and CH_AH_B), 1.8–1.65 (2H, m, CH_2), 1.58–1.39 (2H, m, CH and CH_AH_B), 1.20–0.87 (3H, m, CH_2 and CH), 0.95 (3H, d, *J* = 6.4 Hz, CH_3CH), 0.94 (3H, d, *J* = 7 Hz, CH_3CH), 0.81 (3H, d, *J* = 6.9 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.6, 76.3, 46.9, 40.4, 34.1, 31.3, 26.1, 26.0, 23.4, 21.8, 20.6, 16.2.

4.3. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(diethoxyphosphoryl)acetate 6

A mixture of bromoacetate **5** (5.3 g, 19.1 mmol) and triethylphosphite (3.28 mL, 19.1 mmol) was heated at 100 °C under an inert atmosphere for 3 h. The mixture was cooled to room temperature and the volatiles were removed under high vacuum to give **6** (6.38 g, 100%) as a thick syrup sufficiently pure for the next step. R_f = 0.54 (hexane–EtOAc, 50:50); $[\alpha]_D^{24} = -52.25$ (*c* 1.24, MeOH); IR (film): 2955, 2931, 2870, 1731, 1453, 1390, 1369, 1273, 1115, 1053, 1026, 972, 840, 786 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.76 (1H, dt, *J* = 10.3, 4.4 Hz, OCH), 4.22 (2H, q, *J* = 7.3 Hz, OCH_2), 4.19 (2H, q, *J* = 7.3 Hz, OCH_2), 2.99 (2H, d, *J* = 21.6 Hz, PCH_2), 2.10–1.90 (2H, m, CH and CH_AH_B), 1.80–1.65 (4H, m, CH, CH_2 and CH_AH_B), 1.38 (6H, t, *J* = 7.1 Hz, 2 × OCH_2CH_3), 1.17–0.86 (3H, m, CH and CH_2), 0.94 (6H, d, *J* = 7.2 Hz, CH_3CHCH_3), 0.79 (3H, d, *J* = 7 Hz, $CHCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.6 (d, *J* = 6 Hz), 74.9, 61.9, (d, *J* = 6 Hz), 46.4, 40.2, 34.1 (d, *J* = 132.8 Hz), 33.7, 30.9 (2C), 25.3, 22.7, 21.4, 20.2, 15.8, 15.7, 15.5.

4.4. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate 7

Phosphorus pentachloride (11.9 g, 57 mmol) was added portionwise to the phosphonate **6** (6.34 g, 19 mmol) at 0 °C over 5 min after which the mixture was then heated at 75 °C for 14 h. The reaction mixture was then brought to room temperature and placed under high vacuum to remove volatiles. The residue was dissolved in benzene (40 mL), cooled to 0 °C and 2,2,2-trifluoroethanol (4.15 mL, 57 mmol) was added via a dropping funnel followed by the addition of diisopropylethylamine (9.93 mL, 57 mmol). The reaction mixture was stirred at room temperature for 4 h, poured into ice-water and extracted with benzene. The combined organic extract was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography to provide acetate **7** (4.51 g, 54%) as a thick liquid. R_f = 0.3 (hexane–EtOAc, 85:15); $[\alpha]_D^{24} = -38.0$ (*c* 2.32, MeOH); IR (film): 3019, 2998, 2937, 2877, 1719, 1451, 1418, 1393, 1373, 1298, 1171, 1075, 961, 852, 837, 786 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.74 (1H, dt, *J* = 10.9, 4.4 Hz, OCH), 4.47 (2H, q, *J* = 8.1 Hz, OCH_2), 4.42 (2H, q, *J* = 8.1 Hz, OCH_2), 3.14 (2H, d, *J* = 21.1 Hz, PCH_2), 2.10–1.95 (1H, m, CH), 1.91–1.79 (1H, m, CH), 1.75–1.60 (2H, m, CH_2), 1.50–1.31 (2H, m, CH_2), 1.15–0.81 (3H, m, CH and CH_2), 0.90 (3H, d, *J* = 6.5 Hz, CH_3CH), 0.89 (3H, d, *J* = 6.8 Hz, CH_3CH), 0.75 (3H, d, *J* = 7 Hz, $CHCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.9 (d, *J* = 4.6 Hz), 122.4 (2C, dq, *J* = 275, 5 Hz), 76.4, 62.3 (2C, dq, *J* = 37.50, 5.5 Hz), 46.8, 40.4, 34.0 (1 C, d, *J* = 142 Hz, PCH_2), 33.92, 31.2, 25.9, 23.1, 21.5, 20.3, 15.7.

Please cite this article in press as: Singh, R.; Ghosh, S. K. *Tetrahedron: Asymmetry* (2013), http://dx.doi.org/10.1016/j.tetasy.2013.11.005

4.5. (2*E*,4*E*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-[bis(2,2,2-trifluoroethoxy)phophoryl]-5-phenylpenta-2,4-dienoate 8

A solution of phosphonate **5** (4.5 g, 10.2 mmol), cinnamaldehyde (1.3 mL, 10.2 mmol) and piperidinium benzoate (415 mg, 2 mmol) in benzene (50 mL) was refluxed for 5 h under the Dean–Stark apparatus. The reaction mixture was then brought to room temperature, diluted with water and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the residue was purified by column chromatography to give dienoate **8** (4.45 g, 78%) contaminated with 30% of its (2*Z*)-isomer. A small portion was carefully fractionated to give the individual diastereoisomers in pure form.

Data for (2*E*,4*E*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-[bis(2,2,2-trifluoroethoxy)phophoryl]-5-phenylpenta-2,4-dienoate: R_f = 0.4 (hexane–EtOAc, 85:15); $[\alpha]_D^{23} = -37.1$ (*c* 1.26, MeOH); IR ($CHCl_3$ film): 3018, 2961, 2923, 2868, 1708, 1608, 1579, 1565, 1451, 1415, 1371, 1290, 1254, 1215, 1174, 1104, 1073, 963, 873 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.06 (1H, ddd, *J* = 2.2, 11.6 and 15 Hz, PhCH=C*H*–), 7.74 (1H, dd, *J* = 23.2, 11.4 Hz, P–C=CH), 7.60–7.53 (2H, m, Ph), 7.42–7.38 (3H, m, Ph), 7.17 (1H, d, *J* = 15.3 Hz, PhC*H*), 4.89 (1H, dt, *J* = 10.8, 4.4 Hz, OCH), 4.55–4.28 (4H, m, 2 × OCH_2), 2.13–1.93 (2H, m, CH, CH), 1.80–1.60 (2H, m, CH_2), 1.53–1.39 (2H, m, CH_2), 1.29–0.98 (3H, m, CH and CH_2), 0.93 (3H, d, *J* = 6.4 Hz, CH_3CH), 0.91 (3H, d, *J* = 6.9 Hz, CH_3CH), 0.78 (3H, d, *J* = 6.9 Hz, CH_3CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0 (d, *J* = 15.1 Hz), 157.3 (d, *J* = 31.6 Hz), 148.7, 135.1, 130.3, 128.7 (2C), 128.1 (2C), 123.8 (d, *J* = 20.7), 122.5 (2C, dq, *J* = 275.8, 9.2 Hz), 118.5, 114.6, 62.3 (2C, q, *J* = 38.8 Hz), 46.9, 40.5, 33.9, 31.2, 25.6, 22.8, 21.5, 20.4, 15.4. Anal. Calcd for $C_{25}H_{31}F_6O_5P$: C, 53.96; H, 5.62. Found: C, 54.16; H, 5.66.

Data for (2*Z*,4*E*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-[bis(2,2,2-trifluoroethoxy)phophoryl]-5-phenylpenta-2,4-dienoate: R_f = 0.6 (hexane–EtOAc, 85:15); $[\alpha]_D^{23} = -43.5$ (*c* 0.38, MeOH); IR ($CHCl_3$ film): 2959, 2930, 2864, 1709, 1608, 1578, 1563, 1451, 1286, 1244, 1171, 1102, 1071, 962, 869, 750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (1H, dd, *J* = 39.8, 12 Hz, P–C=CH), 8.07 (1H, ddd, *J* = 15.8, 12 and 3.8 Hz, PhCH=C*H*), 7.63–7.55 (2H, m, Ar), 7.42–7.30 (3H, m, Ar), 7.2 (1H, d, *J* = 15.0 Hz, PhC*H*), 4.86 (1H, dt, *J* = 10.8, 4.3 Hz, OCH), 4.70–4.30 (4H, m, 2 × OCH_2), 2.10–1.98 (1H, m, CH), 1.98–1.85 (1H, m, CH), 1.80–1.62 (2H, m, CH_2), 1.57–1.36 (2H, m, CH_2), 1.20–0.90 (3H, m, CH and CH_2), 0.91 (3H, d, *J* = 6.4 Hz, CH_3CH), 0.90 (3H, d, *J* = 7 Hz, CH_3CH), 0.77 (3H, d, *J* = 7 Hz, CH_3CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.4 (d, *J* = 15 Hz), 158.8 (d, *J* = 10 Hz), 149.6 (d, *J* = 2 Hz), 135.2, 130.6, 128.9 (2C), 128.4 (2C), 123.7 (d, *J* = 6 Hz), 122.6 (2C, dq, *J* = 275, 9 Hz), 115.8 (d, 194 Hz), 76.0, 62.4 (dq, *J* = 38, 5 Hz), 62.3 (dq, *J* = 38, 5 Hz), 47.0, 40.5, 34.1, 31.4, 25.8, 23.0, 21.9, 20.7, 15.8.

4.6. (4*E*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-3-methylene-5-phenyl-4-pentenoate 9

Freshly titrated *n*-butyl lithium (2.5 mL, 1.5 M in hexanes, 3.77 mmol) was added dropwise to a stirred suspension of trimethylsulfonium iodide (0.77 g, 3.77 mmol) in THF (15 mL) at −10 °C. After 20 min at −10 °C, a solution of the phosphonoacetate **8** (mixture of isomers) (0.7 g, 1.26 mmol) in THF (13 mL) was cannulated into the reaction mixture and stirred for 1 h. The reaction mixture was then allowed to gradually return to room temperature, diluted with water and extracted with ethyl acetate. The organic extract was concentrated on a rotary evaporator and the residue was purified by column chromatography to give product **9** (0.463 g, 64%) as a white solid and an inseparable mixture of diastereoisomers in a ratio of 1:1. R_f = 0.3 (hexane–EtOAc, 90:10); IR (film): 3019, 2959, 2929, 2872, 1723, 1600, 1451, 1417, 1296, 1264, 1215, 1173, 1105, 1073, 962, 881, 845, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.22–7.45 (5H, Ph), 6.82 (1H, d, 16.2 Hz, PhCH=C*H*), 6.69 (1H, d, *J* = 16.2 Hz, PhC*H*=CH), 5.60 (s, 1H, C=CH_A, diast-1), 5.59 (s, 1H, C=CH_B, diast-2), 5.57 (s, 1H, C=CH_A, diast-1), 5.56 (s, 1H, C=CH_B, diast-2), 4.73 (1H, dt, *J* = 11, 4.3 Hz, OCH), 4.60–4.25 (5H, m, 2 × POCH_2 and PCH), 2.10–1.90 (1H, m, CH), 1.90–1.69 (1H, m, CH), 1.69–1.55 (2H, m, CH_2), 1.55–1.20 (2H, m, CH_2), 1.10–0.70 (3H, m, CH and CH_2), 0.91 (3H, d, *J* = 6.5 Hz, CH_3CH), 0.79 (3H, d, *J* = 7 Hz, CH_3CH), 0.65 (3H, d, *J* = 6.9 Hz, CH_3CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.3, 136.3, 135.3 (d, *J* = 9 Hz), 130.3, 128.5 (2C), 128.1 (d, *J* = 9.5 Hz), 128.0, 126.6 (2C), 122.4 (2C, dq, *J* = 276, 8.6 Hz), 120.9 (d, *J* = 9.5 Hz, diast-1), 120.8 (d, *J* = 9.2 Hz, diast-2), 76.8 (dist-1), 76.7 (diast-2), 62.9 (2C, dq, *J* = 5.3 and 37.9 Hz, diast-1), 62.8 (2C, dq, *J* = 4.9 and 37.5 Hz, diast-2), 48.4 (d, *J* = 144.6 Hz, diast-1), 48.3 (d, *J* = 144 Hz, diast-2), 46.9 (diast-1), 46.7 (diast-2), 40.4 (diast-1), 40.0 (diast-2), 34.0, 31.3 (diast-1), 31.2 (diast-2), 26.0 (diast-1), 25.8 (diast-2), 23.2 (diast-1), 23.1 (diast-2), 21.6, 20.4 (diast-1), 20.3 (diast-2), 15.9 (diast-1), 15.7 (diast-2).

4.7. (2*Z*,2′*Z*)-Bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2,2′-[(1*R*,2*R*)-2-{(*E*)-styryl}-1,2,3,4-tetrahydro-(1,1′-biphenyl)-2,5-diyl]bis[3-(4-bromophenyl)acrylate] 11

A solution of phosphonate **9** (0.54 g, 0.94 mmol), and 4-bromobenzaldehyde (0.175 g, 0.94 mmol) in THF (8 mL) was cannulated to a suspension of NaH (0.41 g, 55% in oil, 0.94 mmol) in THF (2 mL) at 0 °C and the mixture was stirred for 17 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the residue was purified by column chromatography to give a mixture of two diastereoisomers **11** and **12** (**11**/**12** = 80:20, 0.24 g, 52%). The individual diastereoisomers were separated by preparative thin layer chromatography.

Data for (2*Z*,2′*Z*)-bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2,2′-[(1*R*,2*R*)-2-{(*E*)-styryl}-1,2,3,4-tetrahydro-(1,1′-biphenyl)-2,5-diyl]bis[3-(4-bromophenyl)acrylate] **11**: R_f = 0.6 (hexane–EtOAc, 98:2); mp. 200 °C; $[\alpha]_D^{25} = +156.8$ (*c* 0.31, $CHCl_3$); IR (film): 3023, 2957, 2927, 2869, 1708, 1587, 1486, 1454, 1369, 1215, 1175, 1073, 1011, 981, 913, 811, 757 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$): δ 7.41 (2H, d, *J* = 9.1 Hz, Ar), 7.38 (2H, d, *J* = 8.4 Hz, Ar), 7.27–7.21 (8H, m, Ar), 7.19–7.15 (4H, m, Ar), 7.07 (2H, d, *J* = 8.4 Hz, Ar), 6.59 (1H, s, ArC*H*=C), 6.30 (1H, d, *J* = 16.1 Hz, PhC*H*=CH), 6.29 (1H, s, ArC*H*=C), 6.19 (1H, d, *J* = 16.1 Hz, PhCH=C*H*), 6.04 (1H, d, *J* = 3.5 Hz, PhCHC*H*=C), 4.70 (1H, dt, *J* = 10.5, 4.2 Hz, OCH), 4.61 (1H, dt, *J* = 11.2, 4.9 Hz, OCH), 4.17 (1H, s, broad, PhC*H*CH=C), 2.65–2.58 (1H, m, CH), 2.49–2.43 (1H, m, CH), 2.27 (2H, t, *J* = 5.6 Hz, CH_2), 1.86 (1H, d, broad, *J* = 11.9 Hz, CH), 1.72 (1H, d, broad, *J* = 12.6 Hz, CH), 1.63–1.47 (6H, m, 3 × CH_2), 1.44–1.32 (2H, m, 2 × CH), 1.22 (2H, q, broad, *J* = 11.2 Hz, CH_2), 0.93 (2H, dq, *J* = 12.6, 2.8 Hz, CH_2), 0.82 (3H, d, *J* = 6.3 Hz, CH_3CH), 0.81 (3H, d, *J* = 6.3 Hz, CH_3CH), 0.70–0.78 (2H, m, CH_2), 0.65 (3H, d, *J* = 7 Hz, CH_3CH), 0.64 (3H, d, *J* = 6.3 Hz, CH_3CH), 0.66–0.60 (1H, m, CH_AH$_B$), 0.52–0.47 (1H, m, CH$_A$*H$_B$*), 0.49 (3H, d, *J* = 7 Hz, CH_3CH), 0.42 (3H, d, *J* = 7 Hz, CH_3CH); ^{13}C NMR (175 MHz, $CDCl_3$): δ 168.9 (2C), 141.7, 140.1, 138.3, 137.3, 135.4, 134.9, 133.7, 132.1, 131.4 (2C), 131.2 (2C), 130.7, 130.6 (3C), 130.3, 130.0 (2C), 129.9 (2C), 128.4 (2C), 127.6 (2C), 127.3, 126.8, 126.2 (2C), 124.9, 121.8, 121.5, 75.5, 75.4, 49.4, 46.8, 46.6, 46.5, 40.0 (2C), 33.9, 31.2 (3C), 25.4, 25.3 (2C), 23.0, 22.7, 22.6, 21.9, 21.8, 20.6 (2C), 15.4, 15.3.

Data for (2*Z*,2′*Z*)-bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2,2′-[(1*S*,2*S*)-2-{(*E*)-styryl}-1,2,3,4-tetrahydro-(1,1′-biphenyl)-2,5-diyl]bis[3-(4-bromophenyl)acrylate] **12**: R_f = 0.6 (hexane–EtOAc, 98:2); mp 215 °C; $[\alpha]_D^{25} = -140.6$ (*c* 0.33, $CHCl_3$); IR (film): 3082, 3025, 2952, 2867, 1708, 1487, 1453, 1366, 1214, 1169, 1074, 1011, 981, 910, 875, 811, 761 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$):

δ 7.40 (2H, d, J = 8.4 Hz, Ar), 7.39 (2H, d, J = 7.7 Hz, Ar), 7.28 (2H, d, J = 7.7 Hz, Ar), 7.24–7.20 (6H, Ar), 7.18–7.13 (4H, m, Ar), 7.11 (2H, d, J = 7.7 Hz, Ar), 6.55 (1H, s, ArC*H*=C), 6.38 (1H, s, broad, ArC*H*=C), 6.26 (1H, d, J = 16.8 Hz, PhC*H*=CH), 6.16 (1H, d, J = 16.8 Hz, PhCH=C*H*), 6.01 (1H, d, J = 3.5 Hz, PhCHC*H*=C), 4.70 (1H, dt, J = 10.5, 4.2 Hz, OCH), 4.52 (1H, dt, J = 10.5, 4.2 Hz, OCH), 4.19 (1H, s, broad, PhC*H*CH=C), 2.63–2.56 (1H, m, CH), 2.52–2.45 (1H, m, CH), 2.35–2.31 (1H, m, CH), 2.25–2.21 (1H, m, CH), 1.88 (1H, d, J = 11.9 Hz, CH_AH$_B$), 1.79 (1H, d, J = 11.9 Hz, CH$_A$$H_B$), 1.60 (2H, t, broad, J = 14.7 Hz, CH$_2$), 1.54–1.49 (2H, m, CH$_2$), 1.42–1.34 (2H, m, CH$_2$), 1.32–1.26 (1H, m, CH), 1.25 (1H, t, broad, J = 11.9 Hz, CH), 1.11 (1H, t, broad, J = 11.2 Hz, CH_AH$_B$), 0.94 (1H, dq, J = 13.3, 2.8 Hz, CH$_A$$H_B$), 0.88 (1H, dq, J = 12.6, 2.8 Hz, CH_AH$_B$), 0.79–0.85 (1H, m, CH$_A$$H_B$), 0.76 (3H, d, J = 6.3 Hz, CHCH_3), 0.72–0.79 (2H, m, CH$_2$), 0.69 (3H, d, J = 7 Hz, CHCH_3), 0.62–0.68 (1H, m, CH_AH$_B$), 0.61 (3H, d, J = 7 Hz, CHCH_3), 0.59 (3H, d, J = 6.3 Hz, CHCH_3), 0.57 (3H, d, J = 7 Hz, CHCH_3), 0.55–0.49 (1H, m, CH$_A$$H_B$), 0.48 (3H, d, J = 7 Hz, CHCH_3); ^{13}C NMR (175 MHz, $CDCl_3$): δ 169.32, 169.09, 142.0, 140.2, 138.3, 137.2, 135.7, 135.0, 133.7, 132.0, 131.5 (2C), 131.4 (3C), 130.8 (2C), 130.3, 129.9 (2C), 129.6 (2C), 129.3, 128.4 (2C), 127.6 (2C), 127.3, 126.9, 126.2 (2C), 124.6, 121.8, 121.6, 75.5, 75.4, 49.2, 46.9, 46.7, 46.5, 40.5 (3C), 34.0, 33.9, 31.3, 31.2, 25.2, 24.7, 23.0, 22.7, 22.6, 21.9, 21.7, 20.9, 20.8, 15.8, 15.7; Anal. Calcd for $C_{58}H_{66}Br_2O_4$: C, 70.58; H, 6.74. Found: C, 70.46; H, 6.98.

Acknowledgements

The authors are grateful to Professor Shaikh M. Mobin, Single Crystal X-ray Diffraction Facility, Sophisticated Instrumentation Centre, Indian Institute of Technology, Indore, India for single crystal X-ray diffraction and structural analyses.

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