An Efficient Asymmetric Synthesis of Tarchonanthuslactone[1]

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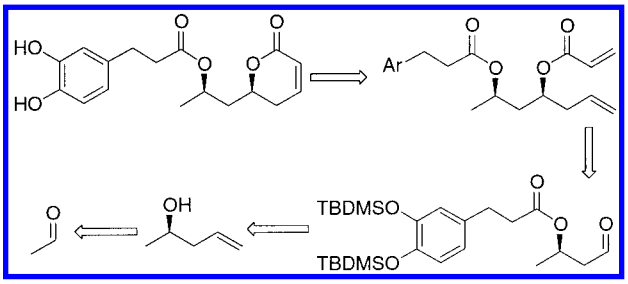
Introduction

α-Pyrones (5,6-dihydro-2*H*-pyran-2-ones) are found in several natural products and have a wide variety of applications. They act as plant growth inhibitors, feeding deterrents, antibacterial, and antitumor agents.[2] These pyrones can be readily transformed to other functional groups, providing new target molecules.[3] Accordingly, several multistep syntheses of such molecules have been reported.[4]

To demonstrate the utility of pinane-based versatile organoboranes[5] for the syntheses of natural products and medicinally active molecules, we undertook the synthesis of pyrone-containing molecules.[6] The title compound, tarchonanthuslactone (**1**) is a dihydrocaffeic acid ester that has been isolated from a compositae, *Tarchonanthus trilobus*.[7] Caffeic acid has been established as active principle to lower plasma glucose in diabetic rats.[8] Nakata and co-workers determined the stereostructure of **1** via a multistep synthesis, starting with optically active 1,3-butanediol.[9] Although this molecule has not been tested, several lactones from Compositae family have been shown to have significant medicinal properties.[10] Consequently, there have been several other approaches to synthesize (−)-**1** as well. For example, Mori and co-workers synthesized this from a chiral dithiane using a 16-step sequence.[11] Solladie and co-workers utilized a chiral sulfoxide to induce the chirality during their 12-step synthesis of **1**.[12] All of the above procedures for **1** involved an asymmetric substrate-controlled synthetic methodology.

Scheme 1



Asymmetric allylboration with *B*-allyldiisopinocampheylborane[13] has been utilized in crucial steps in a large number of syntheses.[14] Also, ring-closing metathesis has been recently applied for the synthesis of lactones of different ring sizes contained in several target molecules.[15] However, there have been very few attempts to combine these two protocols for the convenient syntheses of unsaturated and saturated lactones.[16] Following is the discussion of a seven-step, reagent-controlled synthesis of **1**.

Results and Discussion

Our retrosynthetic analysis is outlined in Scheme 1. We envisaged the synthesis of **1** via a double asymmetric allylboration and ring-closing metathesis reactions as key steps.

Asymmetric allylboration of acetaldehyde with (−)-*B*-allyldiisopinocampheylborane (**2**) in Et_2O−pentane (1:1) at −100 °C yielded the previously reported[13] (*R*)-(+)-4-penten-2-ol (**3**) in 71% yield. The enantiomeric excess (ee) was determined as 94% by comparing the optical rotation

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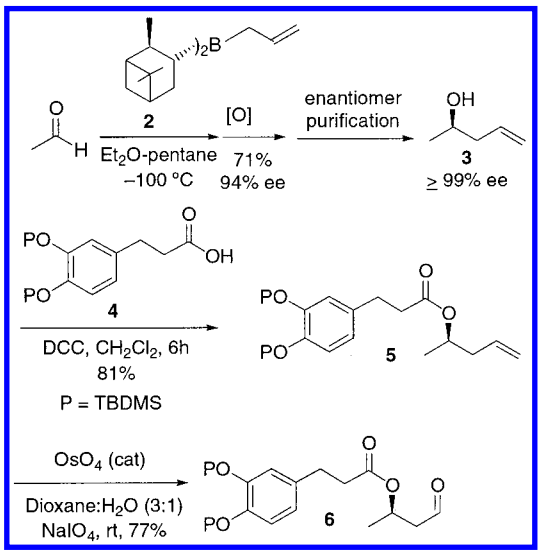
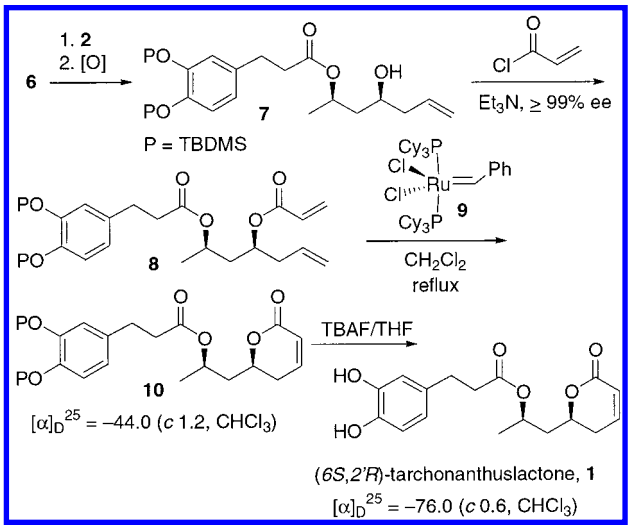
Scheme 2



Scheme 3



with that reported in the literature.[13] Recrystallizing the 3,5-dinitrobenzoate of **3** and recovering the alcohol by basic hydrolysis increased the enantiomeric purity to >99%. Treatment of **3** with TBDMS-protected dihydrocaffeic acid (**4**)[11,12] provided the corresponding ester **5** in 81% yield. Osmylation of this olefin ester, followed by periodate cleavage, provided the aldehyde ester **6** in 77% yield. A second allylboration with (−)-**2** furnished the corresponding enantiomerically pure homoallylic alcohol **7**, which was esterified with acryloyl chloride to provide diester **8**. The synthesis of TBDMS-protected ester **10** was achieved via a ring-closing metathesis in refluxing dichloromethane using Grubbs's bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (**9**)[17] in 46% overall yield from **6**. Deprotection of **10** was carried out with tetrabutylammonium fluoride in THF at room temperature to provide **1** in 80% yield. The sign and value of the optical rotations as well as the spectral characteristics of **10** and **1** matched very well with those reported in the literature.[9,11,12] In conclusion, we have carried out a reagent-controlled asymmetric synthesis of a naturally occurring 6-substituted-5,6-dihydro-2*H*-pyran-2-one, tarchonanthuslactone, in 7.7% overall yield. The salient features include asymmetric allylboration using *B*-allyldiisopinocampheylborane and ring-closing metathesis using Grubbs's ruthenium catalyst. We believe that this reaction sequence is considerably shorter than several procedures currently reported in the literature for the synthesis of **1**.

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Experimental Section

General Methods. All operations were carried out under an inert atmosphere. Techniques for handling air- and moisture-sensitive materials have been previously described.[18] The ^{1}H, ^{11}B, and ^{13}C NMR spectra were plotted on a Varian Gemini-300 spectrometer with a Nalorac-Quad probe. Mass spectra were recorded using with a Hewlett-Packard 5989B mass spectrometer/5890 series II gas chromatograph or a Finnigan mass spectrometer model 4000. CI gas used was isobutane. The optical rotations were measured using a Rudolph Autopol III polarimeter.

Materials. Anhydrous ethyl ether (Et_2O) purchased from Mallinckrodt, Inc. was used as received. CH_2Cl_2 was distilled over CaH_2. DIP-chloride,[19] allylmagnesium bromide, acetaldehyde, osmium tetraoxide, sodium metaperiodate, tetrabutylammonium fluoride, and acryloyl chloride, etc., were all obtained from the Aldrich Chemical Co. Grubbs's catalyst was obtained from Strem Chemicals.

Preparation of (*R*)-4-Penten-2-ol (3). Allylmagnesium bromide (72.6 mL, 1.0 M, 72.6 mmol) was added dropwise to a well-stirred solution of (+)-DIP-chloride (24.45 g, 76.2 mmol) in Et_2O (200 mL) at −78 °C. The mixture was then stirred for 0.5 h at −78 °C, allowed to warm to room temperature, and stirred for 4 h. The solvent was removed under aspirator vacuum, and the residue was extracted with pentane (3 × 150 mL), filtered through a Kramer filter,[18] and concentrated to afford $^{t}Ipc_2BAll$ (**3**) (^{11}BNMR δ 79 ppm) in essentially quantitative yield. The reagent was dissolved in pentane to make a 1 M solution. A 55 mmol (55 mL) amount of the above $^{t}Ipc_2BAll$ was dissolved in Et_2O (55 mL) and cooled to −100 °C. A solution of acetaldehyde (2.2 g, 50 mmol) in anhydrous Et_2O (5 mL) was added dropwise, and the reaction mixture was stirred at −100 °C for 1 h when the reaction was complete (^{11}B NMR shift from δ 79 to δ 52). Addition of methanol (1 mL) to this intermediate, followed by the usual workup with NaOH and H_2O_2, afforded the crude product which was extracted with Et_2O, washed with brine, and dried over anhydrous $MgSO_4$. Distillation (bp 115 °C) provided 3.05 g (71%) of (*R*)-(−)-4-penten-2-ol (**3**) as a liquid. The rotation $[\alpha]^{24}_D$ −9.18 (*c* 5.6, Et_2O) revealed it to be 94% optically pure.

Enantiomer Purification of 3. 3,5-Dinitrobenzoyl chloride (17.25 g, 75 mmol) was added to the above alcohol (4.3 g, 50 mmol) dissolved in CH_2Cl_2 (100 mL). The flask was cooled to 0 °C, followed by the addition of Et_3N (15 g, 150 mmol). The mixture was stirred at room temperature for 2 h, filtered through a pad of silica, concentrated, and chromatographed over silica (hexanes:EtOAc 98:2) to obtain 11.7 g (84%) of the dinitrobenzoate. This was recrystallized from hexanes, dissolved in 25 mL of methanol, and stirred at 0 °C for 2 h with 12 mL of 3 N NaOH. Quenching the reaction with dilute HCl (1%, 50 mL), followed by extraction with ether (3 × 50 mL) and purification by distillation (bp 115 °C), provided 2.01 g (56%) of optically pure (*R*)-(−)-4-penten-2-ol. $[\alpha]^{24}_D$ −9.84 (*c* 3.1, Et_2O).

Preparation of 5. Alcohol **3** (2.15 g, 25 mmol) and TBDMS-protected dihydrocaffeic acid[11,12] (10.25 g, 25 mmol) were dissolved in 50 mL of CH_2Cl_2 in a 250 mL round-bottomed flask and cooled to 0 °C. DCC (35 mL, 1.0 M solution in CH_2Cl_2) and DMAP (0.3 g, 2.5 mmol) were added dropwise to the above mixture and stirred at room temperature for 2 h, filtered through a pad of silica gel, and concentrated under vacuum to obtain

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crude **5**. Silica gel column chromatography (hexane:ethyl acetate 99:1) provided 9.7 g (81%) of pure **5**. IR: ν_{max} cm^{-1} (neat): 2932, 2851, 1732, 1575. MS: EI: *m*/*z*: 478 (M^+), 421, 179, 73 (100%). CI: *m*/*z*: 479 $(M + H)^+$ (100%).

Osmolysis of 5. OsO_4 (0.25 g,1 mmol) was added to the olefinic ester **5** (4.8 g, 10 mmol) dissolved in dioxane:water (3:1, 1.2 L). The reaction mixture was stirred for 0.5 h, followed by the slow addition of $NaIO_4$ (6.42 g, 30 mmol) over a period of 5 min. The mixture was kept stirring for 2 h at room temperature, and the product was extracted with Et_2O (3 × 100 mL), washed with water (250 mL), and purified by column chromatography (silica gel, hexane: EtOAc (9:1)) to obtain 3.7 g (77%) of **6**. IR: ν_{max} cm^{-1} (neat): 2931, 2851, 1731, 1505. Ms: EI: *m*/*z*: 480 (M^+), 353, 221, 179, 73 (100%). CI: *m*/*z*: 481 $(M + H)^+$ (100%).

Allylboration of Aldehydic Ester 6. Aldehyde **6** (4.8 g, 10 mmol) was added to a stirred solution of Ipc_2BAll (22 mL of 0.5 M solution in Et_2O−pentane) at −100 °C and maintained at that temperature for an additional 1 h. The reaction was followed by ^{11}B NMR spectroscopy. Upon completion, the mixture was worked up with $NaOH/H_2O_2$ and extracted with Et_2O. The crude product **7** was used as such for the esterification step.

Preparation of Acryloyl Ester of 7. The above mixture of **7** was dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C, and 4.05 g (45 mmol) of acryloyl chloride and 9.9 g (90 mmol) of Et_3N were added, warmed to room temperature, and stirred for 4 h. The resulting mixture was filtered through a short pad of Celite to remove solid $Et_3N{\cdot}HCl$ and poured into water, and the product was extracted with CH_2Cl_2. The crude product was filtered through a short pad of silica gel and was used directly for the ring-closing metathesis.

Ring-Closing Metathesis of 8. Grubbs's catalyst (**9**) (0.82 g, 1.0 mmol, 10 mol %) was dissolved in 10 mL of CH_2Cl_2 and was added dropwise to a refluxing solution of the above acrylic ester in 800 mL of CH_2Cl_2. Refluxing was continued for 12 h by which time all of the starting material was consumed (TLC). The solvent was removed under aspirator vacuum, and the crude product was purified by silica gel column chromatography (hexane:ethyl acetate 80:20) to obtain 2.53 g (46% overall from **6**) of **10**.

Preparation of Tarchonanthuslactone. α-Pyrone **10** (0.274 g, 0.5 mmol) and benzoic acid (0.18 g, 1.5 mmol) were dissolved in THF (5 mL), followed by the dropwise addition of TBAF (1.25 mL, 1.0 M solution in THF). The mixture was stirred at room temperature for 1 h, concentrated, and extracted with ethyl acetate (3 × 50 mL). Evaporation of the solvent and purification by silica gel column chromatography (hexane:EtOAc 6:4) afforded 0.13 g (80%) of **1** as a gummy liquid. IR: ν_{max} cm^{-1} (neat): 3412, 1691, 1611, 1515. MS: EI: *m*/*z*: 320 (M^+), 123 (100%). CI: *m*/*z*: 321 $(M + H)^+$ (100%).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **1**, **5**, **6**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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