

An Efficient Asymmetric Synthesis of Tarchonanthuslactone¹

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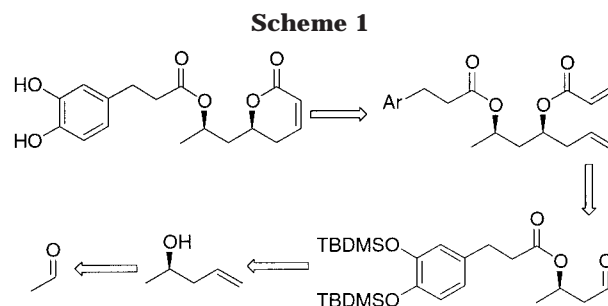
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Introduction

α -Pyrones (5,6-dihydro-2H-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 organoboranes⁵ 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.

Asymmetric allylboration with *B*-allyldiisopinocampheylborane¹³ 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 Et₂O–pentane (1:1) at –100 °C yielded the previously reported¹³ (*R*)-(+)-4-penten-2-ol (**3**) in 71% yield. The enantiomeric excess (ee) was determined as 94% by comparing the optical rotation

(1) Publication No. 11 from Herbert C. Brown Center for Borane Research.

(2) Davies-Coleman, M. T.; Rivett, D. E. A. *Fort. Chem. Org. Natur.* **1989**, *55*, 1.

(3) Reddy, M. V. R.; Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **2001**, in press.

(4) (a) Gopalan, A. S.; Jacobs, H. K. *Tetrahedron Lett.* **1990**, *31*, 5575.

(b) Sato, M.; Sakaki, J. I.; Sugita, Y.; Nakano, T.; Kaneko, C. *Tetrahedron Lett.* **1990**, *31*, 7463. (c) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4117. (d) Sato, T. *Heterocycles* **1986**, *24*, 2173.

(e) Dupont, J.; Donato, A. J. *Tetrahedron Asymmetry* **1998**, *9*, 949. (f) Haase, B.; Schneider, M. P. *Tetrahedron Asymmetry* **1993**, *4*, 1017.

(g) Takano, S.; Setoh, M.; Ogasawara, K. *Tetrahedron Asymmetry* **1992**, *3*, 533. (h) Bonini, C.; Pucci, P.; Racioppi, R.; Viggiani, L. *Tetrahedron Asymmetry* **1992**, *3*, 29. (i) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron Lett.* **1984**, *40*, 1370. (j) Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1990**, *31*, 4761. (k) Yoshida, T.; Saito, S. *Chem. Lett.* **1982**, 1587.

(l) Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335. (m) Bennet, F.; Knight, D. W.; Fenton, G. J. *Chem. Soc., Perkin Trans. 1* **1991**, 1543. (n) Rahmann, S. S.; Wakefield, B. J.; Roberts, S. M.; Dowle, M. D. *J. Chem. Soc. Chem. Commun.* **1989**, 303. (o) Fuganti, C.; Fantoni, G. P.; Sarra, A.; Servi, S. *Tetrahedron Asymmetry* **1994**, *5*, 1135. (p) Sam, T. W.; Yeu, C. S.; Matsjeh, S.; Gan, E. K.; Razak, D.; Mohamed, A. L. *Tetrahedron Lett.* **1987**, *28*, 2541. (q) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1986**, *27*, 5201. (r) Bennet, F.; Knight, D. W. *Tetrahedron Lett.* **1988**, *29*, 4625.

(s) Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281. (t) Bennet, F.; Knight, D. W.; Fenton, G. J. *Chem. Soc., Perkin Trans. 1* **1991**, 519. (u) Honda, T.; Kametani, T.; Kanai, K.; Tatsuzaki, Y.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1733. (v) Keck, G. E.; Li, X. Y.; Knutson, C. E. *Org. Lett.* **1999**, *1*, 411.

(5) Brown, H. C.; Ramachandran, P. V. in *Advances in Asymmetric Synthesis*; Hassner, A., Ed. JAI Press: Greenwich, CT, 1995; Vol. 1, Chapter 5.

(6) (a) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19. (b) Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 583. (c) Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *J. Ind. Chem. Soc.* **1999**, *76*, 939.

(7) Bohlmann, F.; Suwita, A. *Phytochemistry* **1979**, *18*, 677.

(8) Hsu, F. L.; Chen, Y. C.; Cheng, J. T. *Planta Medica* **2000**, *66*, 228.

(9) Nakata, T.; Hata, N.; Iida, K.; Oishi, T. *Tetrahedron Lett.* **1987**, *28*, 5661.

(10) Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Medica* **2000**, *66*, 199.

(11) (a) Mori, Y.; Suzuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1809. (b) Mori, Y.; Kageyama, H.; Suzuki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2574.

(12) Solladie, G.; Gressot-Kempf, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2371.

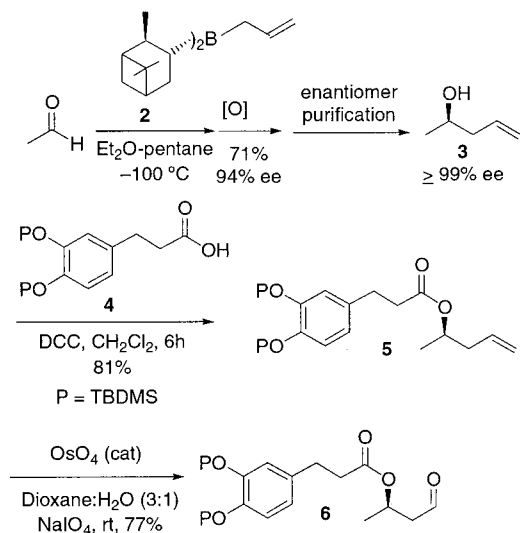
(13) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

(14) Representative examples: (a) Smith, A. B.; Cgen, S. S. Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 10935. (b) Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095. (c) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753.

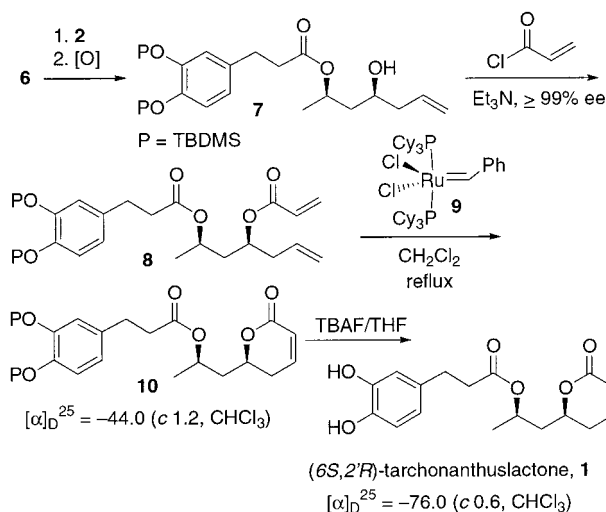
(15) For a recent review see: Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(16) Nicolaou, K. C.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960.

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-2H-pyran-2-one, tar-

chonanthuslactone, in 7.7% overall yield. The salient features include asymmetric allylboration using *B*-allyl-diisopinocampheylborane 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**.

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 ¹H, ¹¹B, and ¹³C 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 (Et₂O) purchased from Mallinckrodt, Inc. was used as received. CH₂Cl₂ was distilled over CaH₂. DIP-chloride,¹⁹ allylmagnesium bromide, acetaldehyde, osmium tetroxide, 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 Et₂O (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 ¹pc₂BAL (**3**) (¹¹B NMR 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 ¹pc₂BAL was dissolved in Et₂O (55 mL) and cooled to –100 °C. A solution of acetaldehyde (2.2 g, 50 mmol) in anhydrous Et₂O (5 mL) was added dropwise, and the reaction mixture was stirred at –100 °C for 1 h when the reaction was complete (¹¹B NMR shift from δ 79 to δ 52). Addition of methanol (1 mL) to this intermediate, followed by the usual workup with NaOH and H₂O₂, afforded the crude product which was extracted with Et₂O, washed with brine, and dried over anhydrous MgSO₄. Distillation (bp 115 °C) provided 3.05 g (71%) of (R)-(-)-4-penten-2-ol (**3**) as a liquid. The rotation [α]_D²⁴ –9.18 (c 5.6, Et₂O) 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 CH₂Cl₂ (100 mL). The flask was cooled to 0 °C, followed by the addition of Et₃N (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. [α]_D²⁴ –9.84 (c 3.1, Et₂O).

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 CH₂Cl₂ in a 250 mL round-bottomed flask and cooled to 0 °C. DCC (35 mL, 1.0 M solution in CH₂Cl₂) 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

(17) For a review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(18) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975. Reprinted edition, Vol. 1. Aldrich Chemical Co. Inc., Milwaukee, WI, 1997. Chapter 9.

(19) DIP-chloride (*B*-chlorodiisopinocampheylborane) is a Trade-mark of Aldrich Chemical Co. Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.

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 ($\text{M} + \text{H}^+$) (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 ($\text{M} + \text{H}^+$) (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 $\text{NaOH}/\text{H}_2\text{O}_2$ 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 $\text{Et}_3\text{N}\cdot\text{HCl}$ 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 ($\text{M} + \text{H}^+$) (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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