A Concise Stereoselective Total Synthesis of (2*R*,2′*R*)-*threo*-(+)-Methylphenidate via a Ring-Closing Metathesis Protocol[1]

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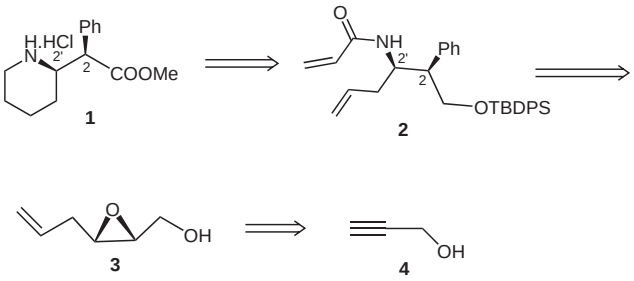
Abstract: In the synthesis of (2*R*,2′*R*)-*threo*-(+)-methylphenidate, a ring-closing metathesis approach was adopted to construct the piperidine ring, while Sharpless asymmetric epoxidation was used for the efficient generation of two contiguous stereocenters.

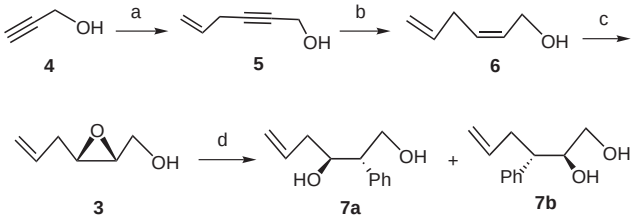
Key words: (2*R*,2′*R*)-*threo*-(+)-methylphenidate, ritalin, attention deficit hyperactivity disorder (ADHD), *cis*-allylic alcohol, Sharpless asymmetric epoxidation, bisolefin, ring-closing metathesis (RCM)

(±)-*threo*-Methylphenidate hydrochloride, commonly called ritalin on the market, is used mainly for the treatment of attention deficit hyperactivity disorder (ADHD) in children in the USA.[2] This medication is also used to treat patients with Narcolepsy (or disorder of sleep regulation). Methylphenidate is a mild stimulant that works by affecting the levels of neurotransmitters in the nervous system. It has been marketed as racemate although the (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride (**1**) is ca. 13 times more active than the corresponding (2*S*,2′*S*)-*threo*-(–)-methylphenidate hydrochloride.[3] Various synthetic approaches for the preparation of the active isomer have been reported including resolution,[4] catalyst-mediated synthesis[5] and few stereoselective syntheses.[6] Amongst the reported syntheses, the enantioselective synthesis by Winkler et al.[5a] using Doyle's rhodium-catalyzed C–H insertion reaction is the shortest. A recent review encompassing all the previous syntheses is worth noting.[5b] Recently we have introduced chiral 2,3-epoxy aldehydes as electrophiles in the diastereoselective Baylis–Hillman reaction[7] and in the Passerini reaction.[8] In continuation of our interest in the use of chiral epoxides, herein we have invoked Sharpless asymmetric epoxidation for generating two contiguous stereocenters and Grubbs' ring-closing metathesis protocol as the key steps towards the total synthesis of methylphenidate **1** (Scheme 1).

Accordingly, chiral piperidine present in **1** was built through the ring-closing metathesis of bisolefin **2**. The amino functional group was introduced by S_N2 mode of the diol which in turn was obtained by the regioselective ring-opening reaction of epoxide **3** by Ph_2CuLi. The appropriate stereoselective epoxide **3** was efficiently prepared from Sharpless asymmetric epoxidation of allylic alcohol obtained by the selective reduction of allylated propargyl alcohol, which in turn could be prepared from the commercially available propargyl alcohol (**4**).



Scheme 1



Scheme 2 *Reagents and conditions*: (a) allyl bromide, CuI, TBAI, K_2CO_3, DMF, r.t., 85%; (b) $Ni(OAc)_2·4H_2O$, ethylenediamine, $NaBH_4$, H_2 atmosphere, EtOH, r.t., 90%; (c) (–)-DIPT, Ti(O*i*-Pr)$_4$, cumene hydroperoxide, CH_2Cl_2, –20 °C, 83%; (d) (i) PhLi, CuI, Et_2O, –40 °C to 0 °C; (ii) $NaIO_4$, MeOH, 73% over two steps.

Thus, propargylic alcohol (**4**; Scheme 2), upon coupling with allyl bromide in the presence of CuI–K_2CO_3–tetrabutylammonium iodide (TBAI) in DMF at room temperature, gave **5** in 85% yield.[9] The triple bond present in **5** was partially reduced in the presence of nickel acetate and catalytic amount of sodium borohydride to afford **6** (90%).[10] Later, **6** on Sharpless asymmetric epoxidation[11] with cumene hydroperoxide in the presence of (–)-diisopropyl D-tartrate and titanium(IV) isopropoxide afforded **3** (83%). The enantiomeric excess of epoxide **3** was calculated to be 92% by correlating with the literature values.[12] Later, chelation-assisted regioselective nucleophilic ring-opening reaction[13] of epoxide **3** with PhLi in the presence of CuI gave the requisite 1,3-diol **7a** (73%) as the major product, while the minor product 1,2-diol **7b** (8%; **7a**/**7b** = 9:1) was removed by oxidative cleavage ($NaIO_4$–MeOH–r.t.).

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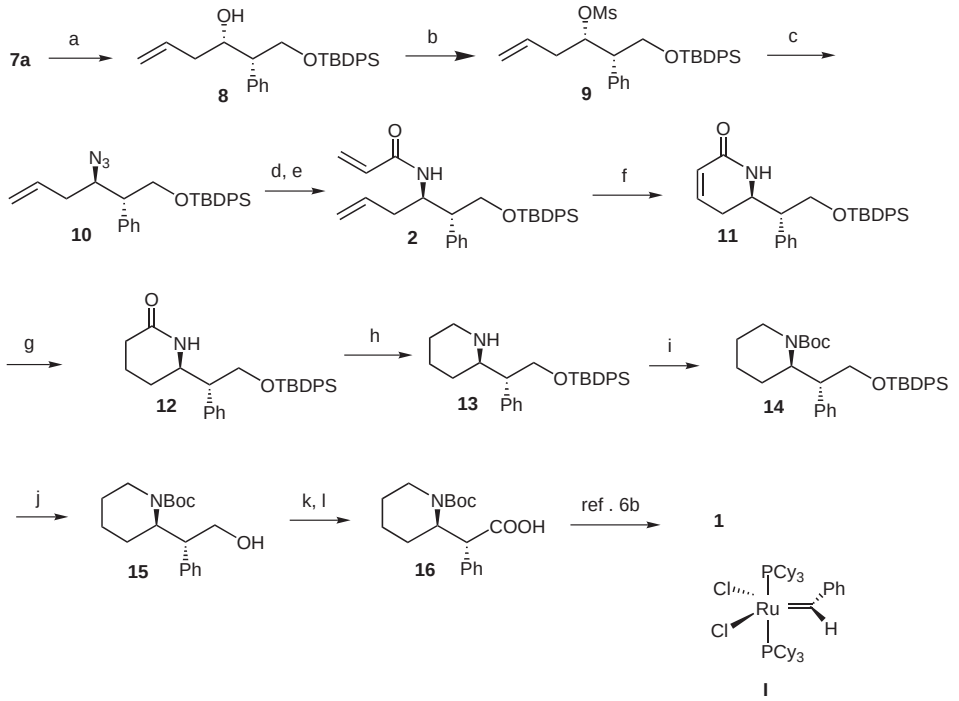

Scheme 3 *Reagents and conditions*: (a) TBDPSCl, imidazole, CH_2Cl_2, r.t., 95%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 87%; (c) NaN_3, DMF, 80 °C, 73%; (d) PPh_3, MeOH, r.t.; (e) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to r.t., 62% over two steps; (f) Grubbs' catalyst (**I**; 15 mol%), CH_2Cl_2, reflux, 75%; (g) Pd/C, H_2 atmosphere, r.t., 86%; (h) (i) BH_3·DMS, THF, 0 °C to r.t.; (ii) EtOH, reflux, 82%; (i) $(Boc)_2O$, Et_3N, THF, 0 °C to r.t., 85%; (j) HF·Py, THF, r.t., 80%; (k) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C; (l) $NaClO_2$, $NaH_2PO_4·2H_2O$, *t*-BuOH–2-methyl-2-butene (2:1), 0 °C to r.t., 12 h, 89% over two steps.

The diol **7a** (Scheme 3) was selectively protected as its TPS ether **8** with TBDPS chloride and the secondary alcohol was then conveniently transformed into amine by a three-step process. Firstly, the secondary alcohol was mesylated (MsCl–Et_3N–CH_2Cl_2, r.t.) which was then converted into the corresponding azide (NaN_3–DMF, 80 °C) via S_N2 pathway. Later, azide **10** was reduced to amine under Staudinger reaction conditions.[14] Initially, a more prudent strategy for constructing the azacyclic part of the molecule was conceived through the reduction of the azide functionality to amine, its conversion into Boc carbamate (Boc_2O–Et_3N–THF, r.t.), allylation of the carbamate as an allyl amide (allyl bromide–NaH–DMF or THF) followed by the ring-closing metathesis reaction. However, it was observed that the highly acidic benzylic proton was easily deprotonated under several allylation reaction conditions resulting in a racemic allylated product. Consequently milder reaction conditions were adopted for the ring construction. The crude amine thus obtained was acryloylated (acryloyl chloride–Et_3N–DMAP–CH_2Cl_2, r.t.) to afford the bisolefin **2** in 62% yield. Ring-closing reaction of **2** was effected using Grubbs' first-generation catalyst (**I**, 15 mol%) in CH_2Cl_2 at reflux temperature to give lactam **11** (75%).[15] Next, in order to transform the α,β-unsaturated lactam into piperidine ring, we tried to reduce both olefin and amide functionalities in a single step with $LiAlH_4$ but observed that the racemization was more facile, and no 1,2- or 1,4-addition products were observed. Hence it was decided to opt for a mild and stepwise reduction of α,β-unsaturated lactam ring. Consequently, the olefin functionality was saturated in the presence of Pd/C in H_2 atmosphere at room temperature and later the amide functionality was efficiently reduced with BH_3·DMS[16] to yield the requisite amine **13** in a very good yield (82%).

Next, amine **13** was protected as its carbamate **14** {85%, $(Boc)_2O$–Et_3N–THF, r.t.} and the silyl group was deprotected with HF·Py at room temperature without any racemization to produce the alcohol **15** (80%).[6b] The required acid **16** was obtained in two consecutive steps. The alcohol was first oxidized to an aldehyde in the presence of Dess–Martin periodinane[17] under basic conditions. The crude aldehyde thus obtained was then oxidized to the acid **16** (89% over two steps) under sodium chlorite oxidation ($NaClO_2$–$NaH_2PO_4·2H_2O$–*t*-BuOH–2-methyl-2-butene) conditions. Treatment of the acid **16** with methanolic HCl at 50 °C yielded the desired (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride (**1**) in 70% yield. All the spectral and analytical data of **1** were identical to those reported previously.[4]

In conclusion, we have described a concise total synthesis of (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride (**1**),[18] the active isomer of ritalin in high optical purity. Herein, we have used Sharpless asymmetric epoxidation for the generation of two contiguous stereocenters and Grubbs' ring-closing metathesis as the key step to construct the piperidine ring. The strategy reported herein is suitable for synthesizing all possible isomers of methylphenidate in enantiopure form or analogues thereof. The present synthesis avoids the use of chiral auxiliary or resolution, thus making it more adoptable.

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References and Notes

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(18) **Spectral Data of Selected Compounds**: Compound **7a**: white solid; mp 49–52 °C; $[\alpha]_D$ –10.30 (*c* = 0.55, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.35 (m, 5 H, ArH), 5.69–5.89 (m, 1 H, olefin), 5.03–5.12 (m, 2 H, olefin), 3.88–4.12 (m, 3 H, OCH, OCH_2), 2.88 (td, *J* = 4.50, 6.73 Hz, 1 H, CHPh), 2.15–2.27 (m, 1 H, allylic), 1.95–2.09 (m, 1 H, allylic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.44, 134.72, 129.37, 128.57, 127.19, 118.13, 71.52, 64.53, 52.55, 39.49. IR (KBr): 3386, 3077, 3028, 2929, 1453, 1037, 915, 703 cm^{-1}. LC–MS: *m*/*z* (%) = 215 (17) [M + 23]. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.40. Compound **10**: $[\alpha]_D$ –26.70 (*c* = 0.75, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.60–7.70 (m, 5 H, ArH), 7.37–7.34 (m, 6 H, ArH), 7.14–7.25 (m, 4 H, ArH), 5.71–5.91 (m, 1 H, olefin), 5.04–5.15 (m, 2 H, olefin), 3.97–4.15 (m, 2 H, CHN_3, CH), 3.74 (dd, *J* = 4.92, 9.85 Hz, 1 H, CH), 2.80–2.89 (m, 1 H, CH), 2.18 (t, *J* = 6.44 Hz, 2 H, allylic), 1.05 (br s, 9 H, *t*-Bu). IR (KBr): 3069, 2931, 2858, 2102, 1427, 1109, 701, 503 cm^{-1}. LC–MS: *m*/*z* (%) = 456 (30) [M + 1]. Anal. Calcd for $C_{28}H_{33}N_3OSi$: C, 73.80; H, 7.30. Found: C, 73.74; H, 7.28. Compound **11**: $[\alpha]_D$ +25.80 (*c* = 0.55, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.62 (m, 4 H, ArH), 7.30–7.41 (m, 6 H, ArH), 7.19–7.25 (m, 3 H, ArH), 7.12 (br s, 1 H, NH), 6.97–7.00 (m, 2 H, ArH), 6.41 (td, *J* = 4.53, 8.69 Hz, 1 H, olefin), 5.86 (d, *J* = 9.82 Hz, 1 H, olefin), 3.96–4.07 (m, 2 H, OCH, NCH), 3.85 (dd, *J* = 3.78, 10.58 Hz, 1 H, OCH), 2.84–2.91 (m, 1 H, CH), 1.93–2.00 (m, 2 H, allylic), 1.09 (br s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.03, 140.24, 135.64, 135.56, 132.62, 129.97, 129.86, 128.79, 128.05, 127.88, 127.8, 127.34, 124.65, 67.67, 54.78, 51.88, 28.89, 26.9, 19.07. IR (KBr): 3370, 2924, 2854, 1675, 1611, 1109, 702 cm^{-1}. LC–MS: *m*/*z* (%) = 456 (34) [M + 1]. Anal. Calcd for $C_{29}H_{33}NO_2Si$: C, 76.44; H, 7.30. Found: C, 76.41; H, 7.28. Compound **13**: $[\alpha]_D$ +21.32 (*c* = 0.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.57 (m, 3 H, ArH), 7.29–7.38 (m, 6 H, ArH), 7.11–7.25 (m, 6 H, ArH), 3.98 (dd, *J* = 6.04, 10.20 Hz, 1 H, OCH_2), 3.89 (dd, *J* = 5.67, 10.58 Hz, 1 H, OCH_2), 2.89–3.06 (m, 2 H, CH_2NH), 2.74–2.81 (m, 1 H, CHNH), 2.60 (td, *J* = 2.64, 11.71 Hz, 1 H, CHPh), 2.19–2.24 (m, 1 H, NH), 1.61 (dd, *J* = 12.84, 43.81 Hz, 2 H, CH_2), 1.17–1.44 (m, 4 H, 2 × CH_2), 1.01 (br s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.30, 135.60, 135.30, 134.80, 129.60, 128.80, 128.20, 127.60, 127.13, 67.40, 62.30, 59.20, 50.90, 45.80, 30.16, 29.60, 26.80, 26.50, 25.60, 24.70, 24.50, 23.40, 22.70, 18.90. IR (KBr): 3356, 2930, 2855, 1427, 1109, 702 cm^{-1}. LC–MS: *m*/*z* (%) = 444 (35) [M + 1]. Anal. Calcd for $C_{29}H_{37}NOSi$: C, 78.50; H, 8.41. Found: C, 78.49; H, 8.44. Compound **15**: white solid; mp 78–80 °C; $[\alpha]_D$ +12.70 (*c* = 0.50, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.37 (m, 5 H, ArH), 4.60 (d, *J* = 12.08 Hz, 1 H), 4.00 (d, *J* = 12.84 Hz, 1 H), 3.66–3.70 (m, 1 H), 3.47–3.55 (m, 2 H), 3.01 (d, *J* = 12.08 Hz, 1 H), 2.84 (d, *J* = 10.8 Hz, 1 H), 1.62–1.66 (m, 2 H), 1.50 (br s, 9 H, *t*-Bu), 1.32–1.43 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.40, 141.20, 128.80, 128.50, 126.70, 80.40, 63.50, 50.20, 45.80, 39.80, 28.40, 26.03, 25.36, 18.80. IR (KBr): 3448, 2928, 2840, 1681, 1598, 1258, 1158 cm^{-1}. LC–MS: *m*/*z* (%): 328 (26) [M + Na]. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91. Found: C, 70.77; H, 8.93. Compound **16**: white solid; mp 115–120 °C; $[\alpha]_D$ = –40.66 (*c* = 0.80, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.46 (m, 5 H, ArH), 4.73–5.03 (m, 1 H, NCH), 4.10 (d, *J* = 11.7 Hz, 1 H, CHPh), 3.88–4.00 (m, 1 H, NCH), 2.85–3.14 (m, 1 H, NCH), 1.72–1.88 (m, 6 H, 3 × CH_2), 1.42 (br s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.90, 154.8, 135.88, 128.80, 128.70, 127.80, 79.88, 54.02, 53.04, 51.17, 39.80, 38.30, 29.67, 28.23, 25.20, 18.80. IR (KBr): 3447, 2924, 2854, 1631, 1260, 760 cm^{-1}. LC–MS: *m*/*z* (%) = 342 (22) [M + 23]. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89. Found: C, 67.66; H, 7.85.