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Concise formal synthesis of (+)-pyripyropene A

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ABSTRACT

A concise enantioselective synthesis of A/B bicyclic segment of naturally occurring α-pyrone meroterpenoid pyripyropene A is achieved in 9 steps (LLS) and 7.5% yield starting from *R*-(−)-carvone. The significant points of the synthesis include: (1) an intramolecular 1, 3-dipolar cycloaddition reaction to construct the A ring and assemble C4 quaternary carbon stereocenter as well; (2) reductive cleavage of the oxazole motif utilized Raney Ni/$B(OCH_3)_3$.

1. Introduction

α-Pyrone meroterpenoids pyripyropenes A–D (Fig. 1, **1**–**4**), isolated from a culture broth of *Aspergillus fumigatus* FO-1289 by Ômura's group in 1993 [1], share a common structure consisting of a naphthol[2,1-b] pyrano[3,4-e] pyran and a pyridine motif. Pyripyropenes A–D are ranked as the most effective naturally occurring in vitro ACAT inhibitors with IC_{50} values of 58, 117, 53, and 268 nM, respectively. And importantly, pyripyropene A (**1**) was proved to be orally active in hamsters, reducing cholesterol absorption by 32%–46% after single doses of 25–75 mg/kg. The intriguing structure and significant pharmacological potential of pyripyropene A have stimulated considerable interests from synthetic communities and continuing studies are focused on both its chemical total synthesis and structure modifications for further SAR research.

Up to now, there are three total syntheses of pyripyropene A reported. In 1995, Ômura, A. B. Smith III and co-workers reported the first total synthesis of (+)-pyripyropene A (Scheme 1, **a**) [2]. They utilized a convergent coupling strategy to combine the sesquiterpene subunit **5** and pyridyl α-pyrone moiety **6**. The requisite coupling segment **5** was efficiently prepared from bicyclic triflate **7** which was derived from (+)-Wieland-Miescher ketone. Subsequently, Ômura and Nagamitsu's group employed a radical cyclization strategy to build the A/B bicyclic enone **9** from which they finished the total synthesis of (+)-pyripyropene A in 2011 (Scheme 1, **b**) [3]. Furthermore, in 2015, Fuse and Takahashi's group reported their total synthesis work of unnatural (−)-pyripyropene A in which the A/B bicyclic motif **11** was successfully prepared from linearly unsaturated epoxide **10** based on a reductive radical polyene cyclization strategy (Scheme 1, **c**) [4]. Recently we reported an efficient synthesis of ABC tricyclic skeleton of octanortriterpenoid malabanone A in which an intramolecular [3 + 2] dipolar cycloaddition reaction was employed to construct the requisite A ring [5a]. A careful comparison of the obtained tricylic oxazole ketone **13** with bicyclic triflate **7** used in Ômura and A. B. Smith III's total synthetic work revealed that they shared a similar 6/6 bicyclic structure and both had the same stereochemistry at C4, C5 and C10. In this context, we became interested in establishing a new and efficient strategy for assembling A/B ring system in pyripyropene A from compound **13**. Herein, we report our synthetic efforts towards this goal.

2. Results and discussions

Our synthesis began from the dialkylation reaction at C10 of *R*-(−)-carvone. As depicted in Scheme 2, the two steps process smoothly afforded acetal **15** with the requisite C10 quaternary carbon stereocenter in 61% overall yield which could be performed on 10 g scale [6]. Subsequent one pot reaction (acidic hydrolysis/condensation with $NH_2OH{\cdot}HCl$) afforded compound **12** in 73% yield. Under the optimized conditions we previously established

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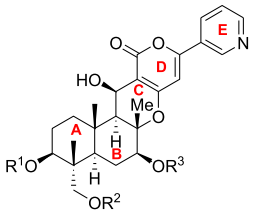


Pyripyropene A (1) $R^1 = R^2 = R^3$= OAc
Pyripyropene B (2) $R^1 = R^3$ = OAc, R^2 = OPr
Pyripyropene C (3) $R^1 = R^2$ = OAc, R^3 = OPr
Pyripyropene D (4) $R^2 = R^3$ = OAc, R^1 = OPr

Fig. 1. Structures of pyripyropenes A–D.

[5a], the intramolecular oxidative 1, 3-dipolar cycloaddition reaction proceeded smoothly to give the tricyclic oxazole **13** in 56% yield at 1 g scale.

With the tricyclic compound **13** in hand, we then turned our attention to its further transformations into the targeted bicyclic vinyl triflate **7** (Scheme 3). Treatment of cyclohex-2-enone **13** with L-selectride followed by oxidative workup afforded ketone **16** in 82% yield [7], which was converted to vinyl triflate **17** upon deprotonation and treatment of the resulting enolate with *N*,*N*-bis(trifluoromethylsulfonyl)aniline [7,8]. The reductive cleavage of the oxazole unit in compound **17** was conducted following a literature precedent [5b]. However, treatment of compound **17** with the reported reagents combination (Raney Ni/B$(OCH_3)_3$) at −78 °C did not give the oxazole ring opening product **18** in our first trial. While the reaction temperature was raised to 30 °C, the desired product **18** was obtained in 72% yield [9]. As the point of departure, stereoselective reduction of the C3 ketone group in compound **18** with tetramethylammonium triacetoxyborohydride in AcOH-CH_3CN furnished the requisite *trans*-diol **19** in satisfied yield and de value (85% yield, >95% de) [2]. Finally [2,8], dibenzylation of **19** yielded the targeted bicyclic vinyl triflate **7** which Ômura and A. B. Smith et al. had used in their elegant convergent total synthesis of (+)-pyripyropene A (**1**) [2]. Meanwhile, we have achieved a formal synthesis of (+)-**1**.

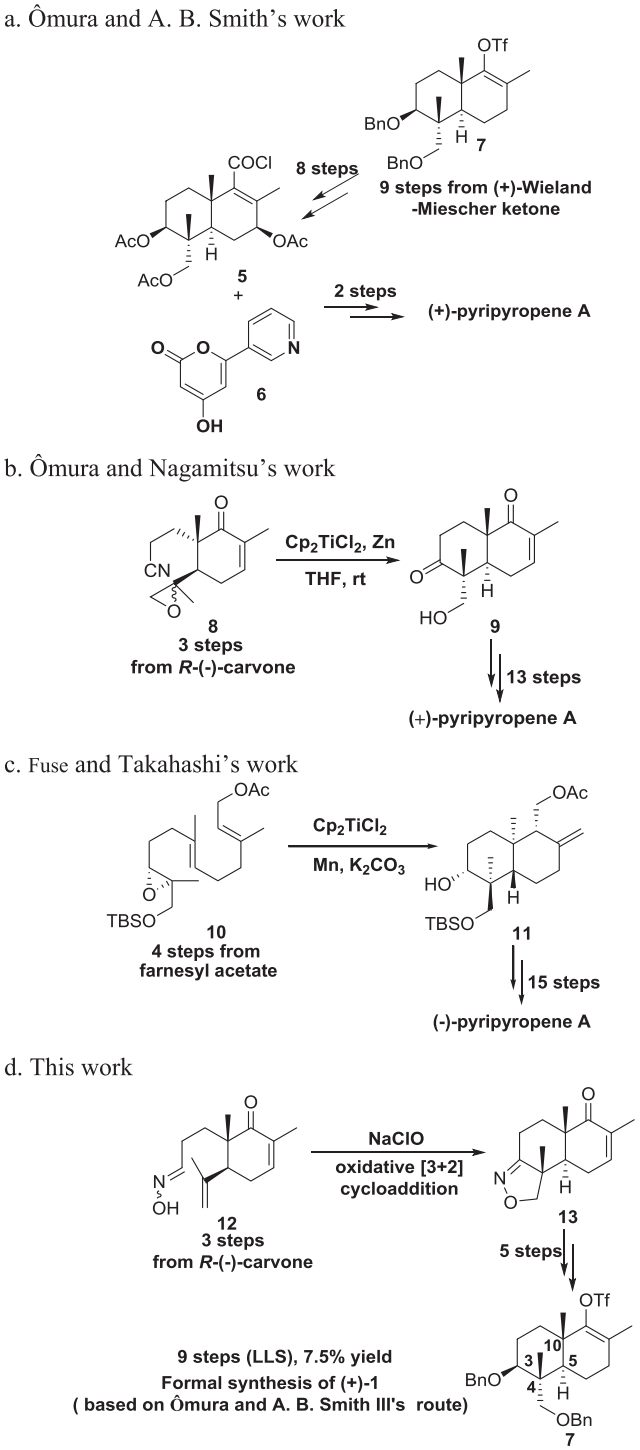
3. Conclusion

5. In summary, an efficient and stereocontrolled preparation of advanced intermediate **7** route to Ômura and A. B. Smith's total synthesis of (+)-pyripyropene A **(1)** has been accomplished in 9 steps and 7.5% overall yield by using (*R*)-(−)-carvone as a cheap chiral starting material. Our synthesis featured an intramolecular 1, 3-dipolar cycloaddition reaction to construct the A ring and assemble C4 quaternary carbon stereocenter as well. Another significant point of our synthesis includes reductive cleavage of the oxazole motif with Raney Ni/B$(OCH_3)_3$. And the application of this strategy for synthesis of other biologically active pyripyropenes is currently underway.

4. Experimental section

4.1. General experimental methods

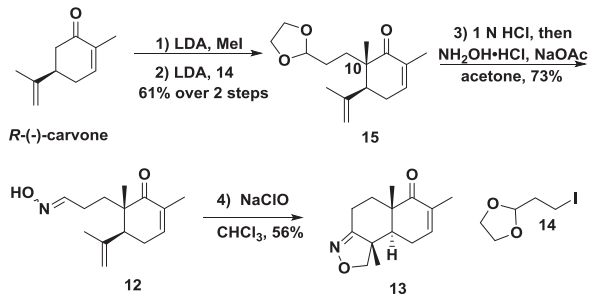
Unless otherwise noted. All reactions sensitive to air or moisture were carried out under argon atmosphere in dry and freshly distilled solvents under anhydrous conditions, column chromatography was performed on silica gel (200–300 mesh). ^{1}H NMR and ^{13}C NMR spectra were obtained using 300 and 75 MHz, 400 and 101 MHz, or spectrometers respectively. Chemical shifts (δ) are given in ppm with reference to solvent signals [^{1}H NMR: $CDCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.0)]. The high resolution mass spectra (HRMS) were recorded on an FT-ICR mass spectrometer using electrospray ionization (ESI). Optical rotations were measured on a precision automated polarimeter. Melting points were measured on a melting point apparatus.



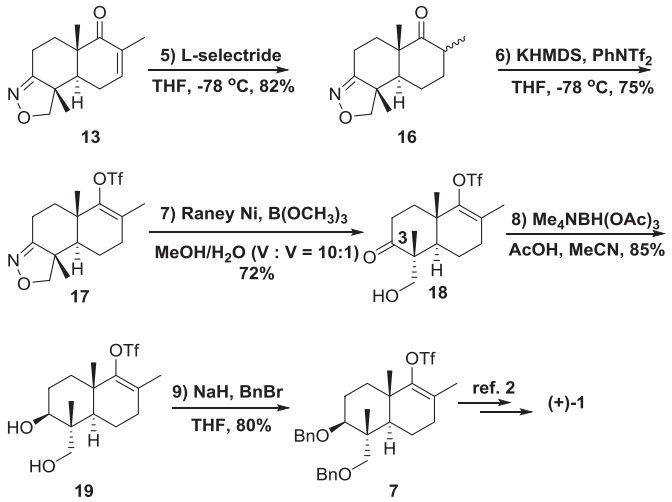
Scheme 1. Total synthesis of pyripyropene A.

4.1.1. Preparation and spectra data of compound *13*

The known compound **13** was prepared according to ref. 5a



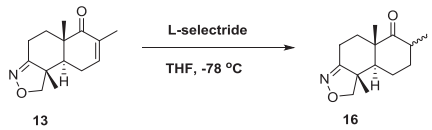
Scheme 2. Synthesis of tricyclic oxazole **13**.



Scheme 3. Synthesis of the bicyclic vinyl triflate **7**.

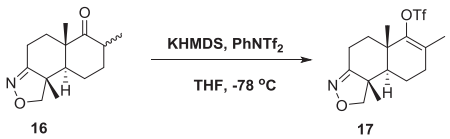
starting from commercially available (*R*)-carvone.

4.1.2. Preparation and spectra data of compound ***16***



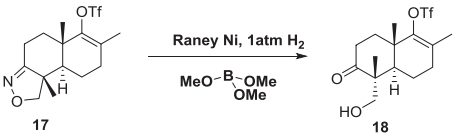
To a solution of enone **13** (1.3 mmol, 304 mg) in THF (20 mL) at −78 °C was added dropwise L-selectride (1.0 M in THF; 1.43 mmol) over 15 min and the resulting colorless solution was stirred at −78 °C for 5 h. The reaction mixture was quenched at −78 °C by successive addition of MeOH (2 mL), aqueous 10% NaOH (1 mL) and aqueous 30% H_2O_2 (1 mL) and the resulting mixture was allowed to slowly warm to rt overnight. The resulting suspension was diluted with H_2O (10 mL) and carefully treated with saturated aqueous $Na_2S_2O_3$ solution (5 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The residual light-yellow oil was purified by column chromatography on silica gel (petro ether/EtOAc, 5:1) to give ketone **16** (251 mg, 82% yield) as a white solid. Mp: 83−86 °C. $[\alpha]_D^{22}$ = −44°(c = 1.0, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.10 (d, *J* = 7.8 Hz, 1H), 3.74 (d, *J* = 7.8 Hz, 1H), 2.75−2.66 (m, 2H), 2.35 (td, *J* = 14.6, 5.0 Hz, 1H), 2.16−2.09 (m, 1H), 2.01 (dd, *J* = 13.1, 3.9 Hz, 1H), 1.93 (ddd, *J* = 14.2, 5.0, 2.4 Hz, 1H), 1.70 (td, *J* = 14.5, 4.7 Hz, 1H), 1.58 (dd, *J* = 12.9, 3.0 Hz, 1H), 1.36 (ddd, *J* = 11.4, 5.7, 3.0 Hz, 1H), 1.31−1.27 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 0.99 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 214.1, 163.6, 83.0, 77.3, 77.0, 76.7, 54.2, 53.7, 48.3, 40.1, 34.9, 32.4, 23.9, 18.6, 18.5, 17.9, 14.7. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{22}NO_2$: 236.1651, found: 236.1645.

4.1.3. Preparation and spectra data of alcohol ***17***



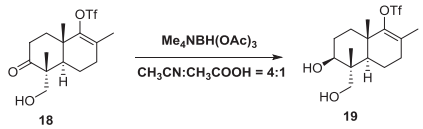
To a stirred solution of **16** (197 mg, 0.84 mmol) in dry THF (25 mL) at −78 °C under Ar was added KHMDS (1.0 M, 2.1 mL) dropwise. The resulting mixture was stirred at −78 °C for 2 h, then it was added the solution of $PhNTf_2$ (749 mg, 2.1 mmol) in 10 mL dry THF. After it was completed, the reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (15 mL × 3). The organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, concentrated to give the crude residue, which was further purified by chromatography on silica gel with EtOAc/petroleum (1 : 20) to afford compound **17** as a colorless oil (231 mg, 75% yield). $[\alpha]_D^{22}$ = 34°(c = 1.0, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.14 (d, *J* = 7.7 Hz, 1H), 3.77 (d, *J* = 7.7 Hz, 1H), 2.71 (ddd, *J* = 15.2, 4.6, 2.3 Hz, 1H), 2.41 (ddd, *J* = 15.2, 13.9, 5.1 Hz, 1H), 2.32−2.17 (m, 2H), 2.13 (ddd, *J* = 13.3, 5.1, 2.3 Hz, 1H), 1.85−1.77 (m, 1H), 1.76 (d, *J* = 1.3 Hz, 1H), 1.74 (s, 3H), 1.47 (td, *J* = 13.5, 4.4 Hz, 1H), 1.38−1.32 (m, 1H), 1.27 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.8, 149.2, 125.7, 120.2, 117.1, 83.6, 77.3, 77.0, 76.7, 53.5, 52.3, 39.3, 33.9, 31.3, 20.7, 18.9, 17.9, 17.8, 17.5. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{21}F_3NO_4S$: 368.1143, found: 368.1138.

4.1.4. Preparation and spectra data of compound ***18***



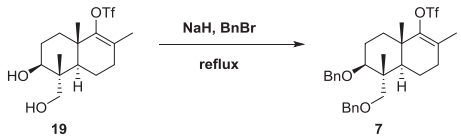
To a solution of **17** (51 mg, 0.14 mmol) in 11 mL of 10:1 MeOH/H_2O were added a wet slurry of Raney nickel (10 mg, 50% in water) and trimethyl borate (0.23 mL, 15 equiv). The suspension was stirred at 30 °C under H_2 (1 atm) for about 1 h. The mixture was filtered through a Celite path and washed with EtOAc (20 mL). The combined filtrate was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography eluting with petroleum ether/ethyl acetate (3:1) to yield compound **18** (colorless oil, 36 mg, 72% yield). $[\alpha]_D^{22}$ = 53°(c = 1.0, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.71 (dd, *J* = 11.2, 6.1 Hz, 1H), 3.37 (dd, *J* = 11.2, 6.6 Hz, 1H), 2.61 (ddd, *J* = 17.1, 12.4, 7.2 Hz, 1H), 2.44 (ddd, *J* = 17.0, 6.3, 2.6 Hz, 1H), 2.32−2.19 (m, 4H), 2.11 (ddd, *J* = 13.4, 7.1, 2.6 Hz, 1H), 1.81 (dd, *J* = 12.8, 6.5 Hz, 1H), 1.76 (s, 3H), 1.69−1.59 (m, 2H), 1.32 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.6, 149.6, 126.2, 120.3, 117.1, 77.3, 77.0, 76.7, 67.0, 52.0, 45.3, 38.7, 35.0, 32.6, 31.6, 18.8, 18.4, 17.4, 16.7. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{22}F_3O_5S$: 371.1140, found: 371.1135.

*4.1.5. Preparation and spectra data of compound **19***



A suspension of tetramethyiammonium triacetoxyborohydride (813 mg, 3.1 mmol) in acetonitrile (16 mL) and acetic acid (4 mL) was cooled to −40 °C and a solution of alcohol **18** (220 mg, 0.62 mmol) in acetonitrile (5 mL) was added dropwise. The mixture was stirred for 3 h at −40 °C, quenched with 0.5 N aqueous potassium sodium tartrate (10 mL), warmed to room temperature, stirred for 30 min, and diluted with CH_2Cl_2 (10 mL). Saturated aqueous $NaHCO_3$ was added dropwise until gas evolution ceased. The organic layer was washed with saturated aqueous $NaHCO_3$, and the organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography eluting with petroleum ether/ethyl acetate (2:1) to yield compound **19** (188 mg, 85% yield) as a colorless oil. $[\alpha]_D^{23} = 38°$(c = 1.0, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.72–3.61 (m, 2H), 3.37 (d, J = 10.5 Hz, 1H), 3.21 (s, 2H), 2.24–2.08 (m, 2H), 1.84 (dt, J = 13.1, 3.2 Hz, 1H), 1.78–1.72 (m, 1H), 1.71 (d, J = 6.5 Hz, 3H), 1.68–1.59 (m, 1H), 1.59–1.51 (m, 2H), 1.40 (ddd, J = 16.9, 11.8, 4.0 Hz, 2H), 1.18 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.0, 124.6, 120.3, 117.1, 77.3, 77.0, 76.7, 75.2, 70.3, 46.1, 41.7, 39.0, 32.7, 31.7, 26.4, 19.1, 18.0, 17.3, 11.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{24}F_3O_5S$: 373.1297, found: 373.1291.

*4.1.6. Preparation and spectra data of compound **7***



A solution of diol **19** (191 mg, 0.53 mmol) in THF (20 mL) was treated with NaH (214 mg of a 60% suspension in mineral oil, corresponding to 5.3 mmol) and the mixture was heated at reflux for 1 h. Neat benzyl bromide (0.63 mL, 5.3 mmol) was added dropwise over 15 min. The reaction was heated at reflux for an additional 4 h, cooled to 0 °C, and carefully quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic solutions were dried over anhydrous Na_2SO_4 and concentrated. And purified by flash chromatography eluting with petroleum ether/ethyl acetate (100:1) to yield compound **7** (234 mg, 80% yield) as a colorless oil. $[\alpha]_D^{23} = 52°$(c = 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (ddd, J = 19.2, 10.8, 5.6 Hz, 10H), 4.60 (d, J = 11.8 Hz, 1H), 4.34 (dt, J = 25.1, 12.2 Hz, 3H), 3.55 (dd, J = 11.8, 4.6 Hz, 1H), 3.37 (d, J = 9.2 Hz, 1H), 3.10 (d, J = 9.2 Hz, 1H), 2.14 (dd, J = 9.9, 4.9 Hz, 2H), 1.96 (dd, J = 13.3, 4.1 Hz, 1H), 1.85 (d, J = 13.6 Hz, 2H), 1.71 (s, 3H), 1.59 (tt, J = 8.7, 4.5 Hz, 1H), 1.54–1.42 (m, 2H), 1.42–1.32 (m, 1H), 1.17 (s, 3H), 0.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.5, 139.2, 138.6, 128.3, 128.2, 127.7, 127.6, 127.5, 127.3, 124.6, 120.3, 117.2, 78.6, 77.3, 77.0, 76.7, 72.9, 71.8, 71.3, 44.5, 42.3, 39.1, 32.6, 31.8, 22.4, 19.2, 17.5, 17.4, 13.3. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{29}H_{36}F_3O_5S$: 553.2236, found: 553.2230. IR (KBr): ν (cm^{-1}) 3363, 2945, 1720, 1638, 1454, 1401, 1248, 1210, 1140, 1104, 891, 738, 698, 605.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.06.017.

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