Catalytic Asymmetric Construction of the exo-7-Aryl-6,8-dioxabicyclo[3.2.1]octane Framework of Psoracorylifols B and C Using a Carbonyl Ylide Cycloaddition Strategy

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Psoracorylifols A-E were isolated from the seeds of Psoralea corylifolia L., which is a well-known traditional Chinese medicine, by Yue and co-workers in 2006. These compounds have been shown to exhibit significant inhibitory activity against two strains of Helicobacter pylori (SS1 and ATCC 43504) at the level of MICs of 12.5 ~ 25 µg/mL, especially against H. pylori-ATCC 43504, a drug-resistant strain with MIC of 128 µg/mL to resist metroniazole. In 2007, Yoshikawa and co-workers independently isolated psoracorylifols B (1) and C (2), possessing a 6,8-dioxabicyclo[3.2.1]octane ring system, from the same seeds.

The 6,8-dioxabicyclo[3.2.1]octane skeleton is a common structural subunit in many biologically active natural products. Among a variety of synthetic routes to such bicyclic ketals, the dirhodium(II)-catalyzed tandem six-membered cyclic carbonyl ylide formation/1,3-dipolar cycloaddition reaction of α-diazo-carbonyl compounds with aldehydes as dipolarophiles is one of the most direct and powerful methods for the construction of this ring system. As a seminal work, Padwa and co-workers reported a concise synthesis of exo- and endo-brevicomins employing the cycloaddition of a six-membered carbonyl ylide derived from 1-diazo-2,5-hexanedione with propionaldehyde in the presence of a catalytic amount of Rh2(OAc)4. Consequently, the development of an enantioselective version of this sequence catalyzed by chiral dirhodium(II) complexes has become a challenging objective. In this process, the chiral dirhodium(II) catalyst must be capable of associating with carbonyl ylide intermediates in the cycloaddition step, because catalyst-free carbonyl ylides are achiral. Recently, we reported catalytic enantioselective 1,3-dipolar cycloadditions of a six-membered carbonyl ylide derived from 1-diazo-5-phenyl-2,5-pentanedi-one (4a) with aromatic aldehydes using dirhodium(II) tetraakis[N-benzene-fused-phthaloyl-(S)-valinate], Rh2(S-BPTV)4 (3), in which electron-deficient dipolarophiles such as 5b and 5c provided exclusively exo cycloadducts 6ab and 6ac in good yields and with up to 92% ee (Scheme 1). As a logical extension of our studies, we addressed a catalytic asymmetric construction of the exo-7-aryl-6,8-dioxabicyclo[3.2.1]octane framework of psoracorylifols B (1) and C (2). Herein, we report exo- and enantioselective cycloadditions of a six-membered carbonyl ylide derived from 1-diazo-6-methyl-2,5-heptanediene (4b) with aromatic aldehydes under the catalysis of Rh2(S-BPTV)4.

Scheme 1. Enantioselective tandem carbonyl ylide formation/1,3-dipolar cycloaddition of 4a with 5a-d catalyzed by Rh2(S-BPTV)4 (3)

This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.
than that with benzaldehyde (74% and 77% ee, entries 3 and 4), whereas the reaction with an electron-rich p-methoxybenzaldehyde (5d) provided a 94:6 mixture of exo and endo cycloadducts 6bd and 7bd in 57% yield with 87% ee for 6bd (entry 6). Thus, we then examined the reaction of p-hydroxybenzaldehyde derivatives 5g and 5h protected as more easily removable methoxymethyl (MOM) or benzyl (Bn) ethers. Gratifyingly, the use of these dipolarophiles 5g and 5h afforded the corresponding exo cycloadducts 6bg and 6bh in similar good yields and high enantioselectivities as those found with 5d (87% and 86% ee, entries 7 and 8). While the discrepancy in reaction mode between carbonyl ylide cycloadditions of 4a and 4b with aromatic aldehydes remains to be elucidated, it is noteworthy that electron-rich and electron-poor aromatic aldehyde dipolarophiles can complement each other in this type of cycloaddition process.

In summary, we have achieved a highly efficient, catalytic asymmetric construction of the exo-7-aryl-6,8-dioxabicyclo[3.2.1]octane framework of psoracorylifols B and C using the 1,3-dipolar cycloaddition reaction of a six-membered carbonyl ylide derived from 1-diazo-6-methyl-2,5-heptanedione with electron-rich aromatic aldehydes under the influence of Rh2(S-BPTV)4. This work, together with the previous finding, demonstrates that the extent of asymmetric induction is highly sensitive to both the substitution pattern (aryl or alkyl substituents) at the ylide carbonyl and the electronic nature of aromatic aldehyde dipolarophiles. Further efforts toward the total synthesis of psoracorylifols B and C are currently underway.

### Experimental Section

Representative procedure for the tandem carbonyl ylide formation/1,3-dipolar cycloaddition (entry 7 in Table 1). Rh2(S-BPTV)4:2THF (3.1 mg, 0.002 mmol, 1 mol %) was added in one portion to a solution of 4b (33.6 mg, 0.20 mmol) and 5h (84.9 mg, 0.40 mmol) in benzotrifluoride (2.0 mL) at 23 °C. After stirring for 5 min, the mixture was concentrated in vacuo. The ratio of 6bh and 7bh was determined to be 95:5 by 1H NMR of the crude product. The residue was purified by column chromatography (silica gel, 1:2 hexane/benzene → 10:1 hexane/ Et2O) to give exo-7-(4-benzyloxyphenyl)-5-isopropyl-6,8-dioxabicyclo[3.2.1]octan-2-one (6bh) (43.3 mg, 0.123 mmol, 62%) as a white solid, along with endo isomer 7bh (1.6 mg, 0.04 mmol, 2%) as a white solid. 6bh: TLC Rf 0.21 (4:1 hexane/ EtOAc); mp 51.5 ~ 53.0 °C for 86% ee; [α]D20 −37.5 (c 1.01, CHCl3) for 86% ee; IR (neat) ν 2968, 1733, 1611, 1585, 1243 cm−1; 1H NMR (400 MHz, CDCl3) δ 1.09 (d, J = 6.9 Hz, 3H, CH(CH3)2), 1.10 (d, J = 6.9 Hz, 3H, CH(CH3)2), 2.09 (ddd, J = 4.6, 8.0, 13.8 Hz, 1H, CH2), 2.24 (heptet, J = 6.9 Hz, 1H, CH(CH3)2), 2.26 (m, 1H, CH2), 2.54 (ddd, J = 1.2, 4.6, 8.0, 16.0 Hz, 1H, COOCH3) 2.61 (ddd, J = 8.0, 8.0, 16.0 Hz, 1H, CH2), 4.41 (s, 1H, COOCH), 4.98 (s, 1H, ArCH), 5.06 (s, 2H, PhCH2O), 6.95 (d, J = 8.6 Hz, 2H, Ar), 7.29 (d, J = 8.6 Hz, 2H, Ar), 7.32-7.43 (m, 5H, ArCH). 13C NMR (100 MHz, CDCl3) δ 17.6 (CH3), 17.9 (CH3), 28.7 (CH2), 32.5 (CH2), 35.6 (CH), 70.0 (CH2), 79.4 (CH), 86.4 (CH), 112.6 (C), 114.8 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.6 (CH), 132.5 (C), 136.8 (C), 159.1 (C), 161.1 (C), 172.5 (C), 173.1 (C), 175.3 (C) ppm.
(C), 158.7 (C), 206.7 (C); EI-HRMS calcd for C22H24O4 (M+) 352.1675, found 352.1673.
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