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Short-step Syntheses of 4-Deoxycarbazomycin B, Sorazolon E, and (+)-Sorazolon E2

Makoto Sako, Kazuya Ichinose, Shinobu Takizawa*, and Hiroaki Sasai*[a]

Abstract: Short-step syntheses of 4-deoxycarbazomycin B and sorazolon E were established through the condensation of cyclohexanone and commercially available 4-methoxy-2,3-dimethylaniline, followed by Pd(II)-catalyzed dehydrogenative aromatization/intramolecular C–C bond coupling and deprotection. A chiral dinuclear vanadium complex (R_a,*S*,*S*)-**6** mediated the first enantioselective oxidative coupling of sorazolon E, affording (+)-sorazolon E2 in good enantioselectivity.

Hydroxycarbazole derivatives (Figure 1) have attracted the interest of many research groups because they exhibit a broad range of biological effects such as antibiotic, antibacterial, and anti-yeast activities, and can act as a free radical scavenger.[1]

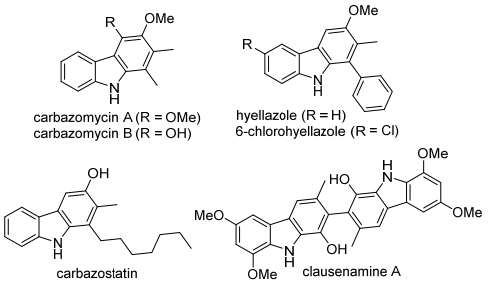

Figure 1. Hydroxycarbazole Derivatives as Natural Products

Among them, sorazolon E (**1**) and E2 (**2**) (dimeric sorazolon E), which are isolated from *sorangium cellulosum* strain soce375, exhibit antibacterial activities (both Gram-positive and Gram-negative), and cytotoxic activity against mouse fibroblast cell line L929.[2] Moody[3] and Knölker[4] independently reported synthesis of **1**, with further contributions by Argade.[5] These groups succeeded in constructing **1** as a synthetic intermediate for carbazomycins and hyellazoles, achieving up to 51% overall yields within eight steps; however, they used highly toxic reagents such as $Hg(OAc)_2$,[3] $Fe(CO)_5$,[4] and $Tl(TFA)_3$.[4b,c] Moreover, in the construction of fully functionalized carbazoles, steric and electronic properties of the carbazole precursors are important for suppressing undesired reactions because of their high reactivities.[1,3-6] The development of a facile and efficient preparation method for functionalized carbazoles by involving bicarbazoles, is a challenging task in contemporary organic synthetic chemistry.

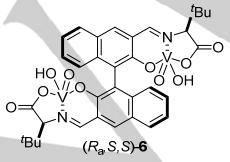

Figure 2. Dinuclear Vanadium Complex (R_a,*S*,*S*)-**6** for the Oxidative Coupling of 2-Naphthol Derivatives

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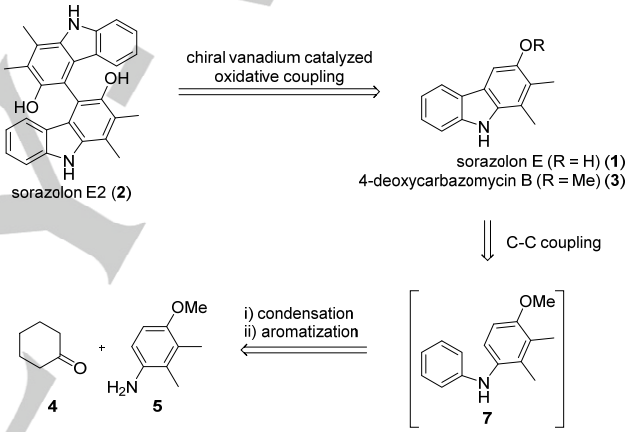
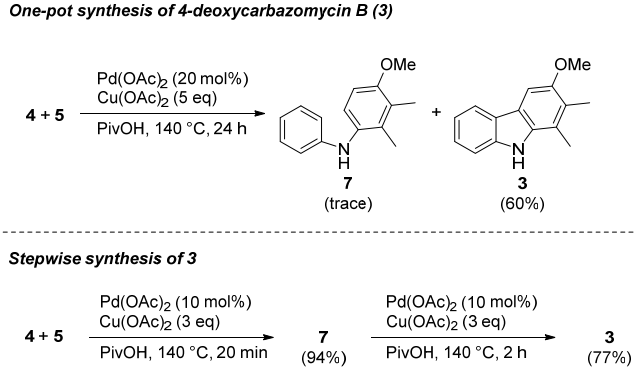
Herein, we report a short step count syntheses of 4-deoxycarbazomycin B (**3**)[3,4b,5,6] and **1** within three steps using cyclohexanone (**4**) and commercially available 4-methoxy-2,3-dimethylaniline (**5**). Chiral dinuclear vanadium complex (R_a,*S*,*S*)-**6** (Figure 2)[7] was used as a catalyst for enantioselective oxidative coupling of **1**, giving (+)-**2** in good yield and enantioselectivity.

As part of our effort to explore domino processes,[8] we were interested in designing sequential reactions to access hydroxycarbazole motifs. As shown in Scheme 1, 4-deoxycarbazomycin B (**3**) could be readily accessed by the condensation of **4** and **5** after metal–mediated dehydrogenative aromatization/intramolecular C–C bond coupling through intermediate **7**.



Scheme 1. Retrosynthesis of Sorazolon E (**1**), Sorazolon E2 (**2**) and 4-Deoxycarbazomycin B (**3**)

So far, we developed a dinuclear vanadium(V) complex (R_a,*S*,*S*)-**6**, which can catalyze the oxidative coupling of 2-naphthols to give the corresponding 1,1'-bi-2-naphthol (BINOL) derivatives in excellent yields with up to 97% ee through a dual activation mechanism.[7] Thus, the complex with two identical vanadium centers in one chiral molecule could activate two molecules of **1**, which is derived from the deprotection of **3**, and thereby, result in the formation of **2** with high enantiocontrol.



Scheme 2. Pd(II)-Catalyzed Synthesis of 4-Deoxycarbazomycin B (**3**)

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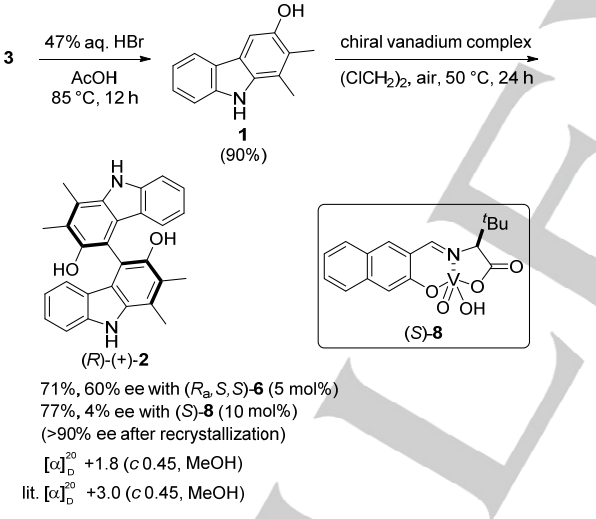
For the synthesis of sorazolons, the one–pot reaction of **4** and **5** with 20 mol% of $Pd(OAc)_2$ and $Cu(OAc)_2$ (5 eq) (as a co-oxidant) in PivOH[9] was first tested. As expected, **3** was formed in 60% yield. A trace amount of carbazole precursor **7** was detected as shown in Scheme 2. Other reaction conditions [$PdCl_2$, $Pd(TFA)_2$, AcOH, and/or O_2 as a co-oxidant] did not show any improvements. As an alternative synthesis of **3**, a stepwise protocol was examined. Decreasing the amount of $Cu(OAc)_2$ (3 eq) with a shorter reaction time (20 min) led to the formation of product **7** in 94% yield. Subsequently, isolated **7** was applied to the palladium-catalyzed intramolecular coupling to give **3** in 77% yield.

To perform enantioselective oxidative coupling[10] of **1**, deprotection of **3** to **1** was achieved using 47% HBr aq. (AcOH, 85 °C, 12 h, 90% yield) as shown in Scheme 3.[11] Although Moody reported the synthesis of rac-**2** *via* oxidative coupling of **1** with dibenzoyl peroxide,[1b,3b] the absolute configuration of **2** has been unclear until now. Moreover, to the best of our knowledge, few reports on the enantioselective oxidative coupling of 3-hydroxycarbazoles have been published. Among the reaction solvents we studied [$(Cl_2CH)_2$, $CHCl_3$, CCl_4, toluene, and H_2O] for an oxidative coupling of **1** using catalyst (R_a,*S*,*S*)-**6** at various reaction temperatures, $(ClCH_2)_2$ at 50 °C provided the highest reaction rate with good enantioselectivity, affording **2** in 71% yield with 60% ee.[12] Finally, >90% ee of **2** was obtained from a mother liquor of the recrystallization. The synthetic sorazolon E2 exhibited a positive optical rotation signal that was the same as in the natural form. The absolute configuration of synthetic sorazolon E2 was assigned the *R*-form after comparison with the CD spectrum of optically pure 9*H*,9'*H*-[4,4'-bicarbazole]-3,3'-diol (BICOL)[13] in 5% DMSO/H_2O. We realized that dinuclear vanadium complex (R_a,*S*,*S*)-**6** could produce the natural sorazolon E2 (absolute configuration).



Scheme 3. Synthesis of Sorazolon E (**1**) and Sorazolon E2 (**2**)

Previously, we described dinuclear vanadium(V) catalyst (R_a,*S*,*S*)-**6** promoted the intramolecular-manner coupling of 2-naphthols to afford (*S*)-configured BINOLs.[7] However, (*R*)-form **2** was obtained when using (R_a,*S*,*S*)-**6** for the coupling of **1**. Since a use of mononuclear vanadium catalyst (*S*)-**8** (10 mol%),[14] for which the facilitation of the intramolecular-manner coupling would be impossible, led to a formation of (*R*)-**2** with similar reaction rate of the dinuclear vanadium complex, the vanadium catalyst (R_a,*S*,*S*)-**6** likely promoted the intermolecular-manner coupling.

In summary, we established short–step synthetic protocols for sorazolon E (**1**), (+)-sorazolon E2 (**2**), and 4-deoxycarbazomycin B (**3**) using palladium and vanadium catalysts. A chiral dinuclear vanadium complex was found to promote the enantioselective oxidative coupling of 3-hydroxycarbazole **1** to give bicarbazole derivate **2** with good enantioselectivity for the first time.

Experimental Section

General information

^{1}H and ^{13}C-NMR spectra were recorded with JEOL JMN LA-400 FT NMR (^{1}H-NMR 400 MHz, ^{13}C-NMR 100 MHz). ^{1}H-NMR spectra are reported as follows: chemical shift in ppm (δ) relative to the chemical shift of $CHCl_3$ at 7.26 ppm or acetone at 2.09 ppm, integration, multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants (Hz). ^{13}C-NMR spectra reported in ppm (δ) relative to the central line of triplet for $CDCl_3$ at 77 ppm. FT-MS spectra were obtained with LTQ Orbitrap XL (Thermo Fisher Scientific). ESI-MS spectra were obtained with JMS-T100LC (JEOL). FAB-MS spectra were obtained with JMS-700 (JEOL). Optical rotations were measured with JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/Vis detector) using a mixture of *n*-hexane and *i*-PrOH or EtOH as eluents. FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100). CD spectra were recorded on a JASCO J-725. Column chromatography on SiO_2 was performed with Kanto Silica Gel 60 (40-100 μm). Commercially available organic and inorganic compounds were used without further purification. The products **1**,[2a] **2**,[2a] and **3**[6b] were identical in all respects with reported in the literatures.

One-pot synthesis of 4-deoxycarbazomycin B (3)[6b]: Cyclohexanone (**4**: 24.5 mg, 0.25 mmol, 1.0 eq.), 4-methoxy-2,3-dimethylaniline (**5**: 43.5 mg, 0.29 mmol, 1.2 eq.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 20 mol%), $Cu(OAc)_2$ (227 mg, 1.25 mmol, 5.0 eq.) and PivOH (1 mL) were added to a test tube equipped with a magnetic stirrer. The reaction vessel was cooled with liquid N_2, degassed under vacuum and refilled with N_2 gas (repeated three times). The reaction mixture was then stirred under N_2 atmosphere at 140 °C for 24 h. After the cooling to room temperature, the reaction mixture was diluted with sat. K_2CO_3 aq. and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 19:1), affording 4-deoxycarbazomycin B (**3**) as an yellow solid (33.6 mg, 60% yield).^{1}H-NMR ($CDCl_3$) δ: 7.99 (1H, d, *J* = 7.4 Hz), 7.77 (1H, s), 7.43-7.35 (3H, m), 7.19 (1H, t, *J* = 7.4 Hz), 3.95 (3H, s), 2.47 (3H, s), 2.34 (3H, s); HRMS (APCI) calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1232, found: 226.1217.

Preparation of 7[6b]: Cyclohexanone (**4**: 9.82 mg, 0.1 mmol, 1.0 eq.), 4-methoxy-2,3-dimethylaniline (**5**: 21.2 mg, 0.14 mmol, 1.4 eq.), $Pd(OAc)_2$ (2.24 mg, 0.01 mmol, 10 mol%), $Cu(OAc)_2$ (54.5 mg, 0.3 mmol, 3.0 eq.) and PivOH (0.4 mL) were added to a test tube equipped with a magnetic stirrer. The reaction vessel was cooled with liquid N_2, degassed under vacuum and refilled with N_2 gas (repeated three times). The reaction mixture was then stirred under N_2 atmosphere at 140 °C for 20 min. After the cooling to room temperature, the reaction mixture was diluted with sat. K_2CO_3 aq. and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 20:1 - 3:1) to afford the desired product **7** as an yellow solid (21.3 mg, 94% yield). ^{1}H-NMR ($CDCl_3$) δ: 7.17 (2H, t, *J* = 7.8 Hz), 7.04 (1H, d, *J* = 8.7 Hz), 6.76 (1H, d, *J* = 7.8 Hz), 6.72 (1H, d, *J* = 8.7 Hz), 6.64 (2H, d, *J* = 7.8 Hz), 5.24 (1H, s), 3.83 (3H, s), 2.20 (3H, s), 2.16 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 154.9, 146.9, 133.9, 133.1, 129.2, 126.2, 122.9, 118.3, 114.3, 108.4, 55.7, 14.5, 12.3; IR (cm^{-1}) 3398, 1603, 1501, 1315; HMRS (APCI) calcd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1388, found: 228.1376.

Synthesis of sorazolon E (1)[2a]: 4-Deoxycarbazomycin B (**3**) (22.5 mg, 0.1 mmol) was dissolved in 47% HBr aq. (0.2 mL) and glacial acetic acid (0.5 mL) under N_2 atmosphere, and the resulting mixture was stirred for 12 h at 85 °C. After the completion of reaction, precipitated residues were collected and washed with water. The obtained solid was dissolved in CH_2Cl_2 and dried over Na_2SO_4. The organic layer was removed under vacuum and the residue was purified by short column chromatography on silica gel (*n*-hexane:EtOAc = 10:1 - 2:1) to afford sorazolon E (**1**) as a white solid (18.9 mg, 90% yield). ^{1}H-NMR (ACETONE-D_6) δ: 9.73 (1H, s), 7.76 (1H, d, *J* = 7.5 Hz), 7.66 (1H, s), 7.27 (2H, t, *J* = 7.5 Hz), 7.13 (1H, t, *J* = 7.5 Hz), 6.92 (1H, t, *J* = 7.5 Hz), 2.37 (3H, s), 2.20 (3H, s); HRMS (APCI) calcd for $C_{14}H_{14}NO$ $[M+H]^+$: 212.1075, found: 212.1063.

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Synthesis of sorazolon E2 (2)[2a]: Sorazolon E (**1**; 8.44 mg, 0.04 mmol) and dinuclear vanadium catalyst (*R*a,*S*,*S*)-**6** (1.5 mg, 0.002 mmol, 5 mol%) were stirred in $(ClCH_2)_2$ (0.2 mL) under air at 50 °C. After 24 h, the reaction mixture was directly purified by PTLC (*n*-hexane:EtOAc = 3:1) to afford sorazolon E2 (**2**) as a white solid (6.0 mg, 71% yield, 60% ee). ^{1}H-NMR (ACETONE-D_6) δ: 9.91 (2H, s), 7.21 (2H, d, *J* = 8.2 Hz), 6.93 (2H, t, *J* = 6.9 Hz), 6.51 (2H, d, *J* = 8.2 Hz), 6.40 (2H, t, *J* = 6.9 Hz), 6.38 (2H, s), 2.53 (6H, s), 2.32 (6H, s); enantiomeric exces: 60%, determined by HPLC (YMC CHIRAL Cellulose-SB, *n*-hexane/*i*-PrOH = 4/1; flow rate 1.0 mL/min; 25 °C; 250 nm) first peak: t_R = 17.3 min, second peak: t_R = 21.3 min; $[\alpha]_D^{20}$ +1.8 (*c* 0.45, MeOH) for 90% ee (*R* isomer).

Acknowledgements

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Keywords: chiral vanadium catalyst • enantioselective oxidative coupling • short-step synthesis • sorazolons • hydroxycarbazole

[1] For reviews on hydroxycarbazoles as natural products a) C. J. Moody, *Synlett* **1994**, 681; b) S. Tasler, G. Bringmann, *Chem. Rec*. **2002**, *2*, 113.

[2] a) S. Karwehl, R. Jansen, V. Huch, M. Stadler, *J. Nat. Prod.* **2016**, *79*, 369; b) J. Herrmann, A. A. Fayad, R. Müller, *Nat. Prod. Rep*. **2017**, *34*, 135.

[3] a) C. J. Moody, P. Shah, *J. Chem. Soc., Perkin Trans. 1* **1989**, 376; b) C. J. Moody, P. Shah, *J. Chem. Soc., Perkin Trans. 1* **1989**, 2463.

[4] a) H.-J. Knölker, M. Bauermeister, D. Bläser, R. Boese, J.-B. Pannek, *Angew. Chem. Int. Ed.* **1989**, *28*, 223; b) H.-J. Knölker, M. Bauermeister, J.-B. Pannek, D. Bläser, R. Boese, *Tetrahedron* **1993**, *49*, 841; c) H.-J. Knölker, M. Bauermeister, J.-B. Pannek, M. Wolpert, *Synthesis* **1995**, 397.

[5] S. B. Markad, N. P. Argade, *Org. Lett*. **2014**, *16*, 5470.

[6] a) T. Kawasaki, Y. Nonaka, M. Akahane, N. Maeda, M. Sakamoto, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1777; b) B. K. Chowdhury, S. Jha, *Synth. Commun*. **2001**, *31*, 1559; c) B.-J. Li, S.-L. Tian, Z. Fang, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2008**, *47*, 1115.

[7] Selected reviews and reports on the chiral vanadium catalysis, see: a) S. Takizawa, *Chem. Pharm. Bull.* **2009**, *57*, 1179; b) S. Takizawa, H. Gröger, H. Sasai, *Chem. Eur. J.* **2015**, *21*, 8992; c) M. Sako, S. Takizawa, Y. Yoshida, H. Sasai, *Tetrahedron: Asymmetry* **2015**, *26*, 613; d) M. Sako, Y. Takeuchi, T. Tsujihara, J. Kodera, T. Kawano, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2016**, *138*, 11481.

[8] a) S. Takizawa, H. Sasai, *J. Synth. Org. Chem. Jpn.* **2014**, *72*, 781; b) M. A. Abozeid, S. Takizawa, H. Sasai, *Tetrahedron Lett.* **2015**, *56*, 4316; c) S. Takizawa, K. Kishi, Y. Yoshida, S. Mader, F. A. Arteaga, S. Lee, M. Hoshino, M. Rueping, M. Fujita, H. Sasai, *Angew. Chem. Int. Ed.* **2015**, *54*, 15511; d) T.-T.-D. Ngo, K. Kishi, M. Sako, M. Shigenobu, C. Bournaud, M. Toffano, R. Guillot, J.-P. Baltaze, S. Takizawa, H. Sasai, G. Vo-Thanh, *ChemistrySelect* **2016**, *1*, 5414; e) S. Takizawa, K. Kishi, M. Kusaba, B. Jianfei, T. Suzuki, H. Sasai, *Heterocycles* **2017**, *95*, 761.

[9] a) H.-R. Bjørsvik, V. Elumalai, *Eur. J. Org. Chem.* **2016**, 5474; b) L. Wen, L. Tang, Y. Yang, Z. Zha, Z. Wang, *Org. Lett.* **2016**, *18*, 1278; c) C. Schuster, M. Rönnefahrt, K. K. Julich-Gruner, A. Jäger, A. W. Schmidt, H.-J. Knölker, *Synthesis* **2016**, *48*, 150; d) S. K. Kutz, A. W. Schmidt, H.-J. Knölker, *Synthesis* **2017**, *49*, 275.

[10] Selected reports on catalytic asymmetric oxidative coupling of phenolic compounds, see: a) M. Nakajima, I. Miyoshi, K. Kanayama, S. Hashimoto M. Noji, K. Koga, *J. Org. Chem*. **1999**, *64*, 2264; b) R. Irie, K. Masutani, T. Katsuki, *Synlett* **2000**, 1433; c) C.-Y. Chu, D.-R. Hwang, S.-K. Wang, B.-J. Uang, *Chem. Commun*. **2001**, 980; d) N. B. Barhate, C.-T. Chen, *Org. Lett.* **2002**, *4*, 2529; e) J. Gao, J. H. Reibenspies, A. E. Martell, *Angew. Chem. Int. Ed.* **2003**, *42*, 6008; f) T. Temma, S. Habaue, *Tetrahedron Lett*. **2005**, *46*, 5655; g) Q.-X. Guo, Z.-J. Wu, Z.-B. Luo, Q.-Z. Liu, J.-L. Ye, S.-W. Luo, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2007**, *129*, 13927; h) J. B. Hewgley, S. S. Stahl, M. C. Kozlowski, *J. Am. Chem. Soc*. **2008**, *130*, 12232; i) H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2009**, *131*, 6082; j) S. K. Alamsetti, E. Poonguzhali, D. Ganapathy, G. Sekar, *Adv. Synth. Catal*. **2013**, *355*, 2803; k) S. Narute, R. Parnes, F. D. Toste, D. Pappo, *J. Am. Chem. Soc.* **2016**, *138*, 16553.

[11] H.-J. Knölker, H. Goesmann, C. Hofmann, *Synlett* **1996**, 737.

[12] The yield (50%) and ee (7%) of **2** were decreased when the reaction was carried out under O_2.

[13] M.-A. Dubois, A. Grandbois, S. K. Collins, A. R. Schmitzer, *J. Mol. Recognit.* **2011** *24*, 288.

[14] The amount of the mononuclear catalyst (*S*)-**8** used was twice to that of (*R*a,*S*,*S*)-**6** because (*S*)-**8** has only one active center.

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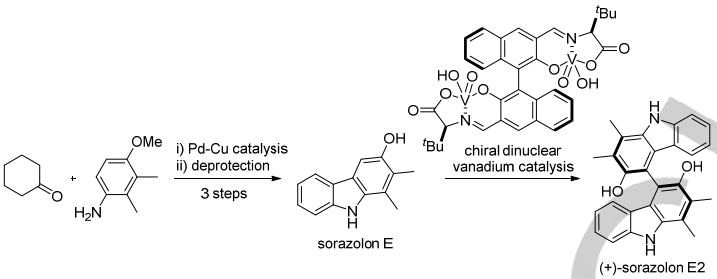
Short–step syntheses of deoxycarbazomycin B, sorazolon E, and (+)-sorazolon E2 were established using palladium and vanadium catalysts. A chiral dinuclear vanadium complex was found to promote the first enantioselective oxidative coupling of the 3-hydroxycarbazole to give the bicarbazole derivate in good enantioselectivity.



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Short-step Syntheses of 4-Deoxycarbazomycin B, Sorazolon E, and (+)-Sorazolon E2