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Synthesis of (±)-cartorimine

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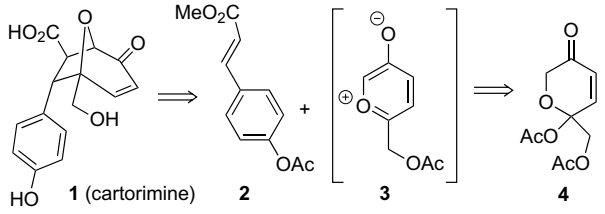
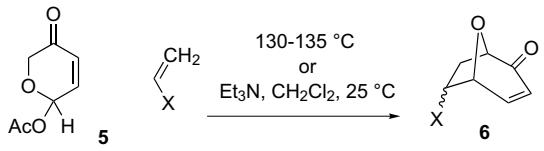
Abstract—Heating pyranulose **4** and cinnamate **2** in the presence of 2,6-di-*t*-butylpyridine in CH_3CN afforded the [5+2] cycloadduct, which was hydrolyzed to give 13% of cartorimine (**1**).

Yin, He and Ye recently isolated the oxabicyclic acid cartorimine (**1**) from *Carthamus tinctorius* L., which is used as a traditional Chinese medicine to promote blood circulation. The structure was established from extensive NMR spectral data interpretation and single crystal X-ray analysis.[1] We thought that **1** could be prepared by the [5+2] cycloaddition of methyl 4-acetoxycinnamate (**2**) with oxypyrylium zwitterion **3**, which could be generated in situ from pyranulose **4** (Scheme 1). This sequence may be related to the biosynthesis of **1** because 4-hydroxycinnamic acid is an abundant natural product and **4** is generated by the dehydration and oxidation of fructose.[2]

Hendrickson and Farina discovered that these [5+2] cycloadditions can be carried out by simply heating **5** and a dipolarophile at 130–135 °C to afford up to 69% of adduct **6** (Scheme 2).[3] This reaction has been extensively developed by Sammes, who found that electron rich



Scheme 1. Retrosynthesis of cartorimine.



Scheme 2.

dipolarophiles were more reactive and that the reactions can also be carried out using Et_3N to generate the oxypyrylium zwitterion at room temperature.[4] Further examples of [5+2] cycloadditions have been reported by Heathcock and Ohmori.[5–7] Sammes reported that reaction of **5**, styrene (6 equiv) and Et_3N in CH_2Cl_2 at 25 °C afforded 65% of **6**, X = *endo*-Ph, which lacks the hydroxymethyl and carboxylic acid groups of cartorimine (**1**). Unfortunately, these substituents will retard the cycloaddition of **2** and **3**. The facile dimerization of the oxypyrylium zwitterion prevents the use of unreactive dipolarophiles so that it was not clear a priori that the synthesis of **1** could be achieved by this route.

5-(Acetoxymethyl)furfural (**7**) was reduced with $NaBH_4$ in EtOH for 10 min at 0 °C. The solution was quenched dropwise with HOAc and concentrated. The residue was taken up in water and treated with bromine in MeOH to give 80% of **8**.[2,8] Acetylation with Ac_2O, pyridine, and DMAP in CH_2Cl_2 afforded the unstable acetate **4**, which was used without purification (Scheme 3). Acetoxy ester **2** was prepared in 94% yield from 4-hydroxycinnamic acid by esterification with methanolic HCl at reflux and acetylation with Ac_2O, pyridine, and DMAP in CH_2Cl_2. Reaction of **2** and **4** with Et_3N in CH_2Cl_2 at 25 °C or with $EtN(i\text{-}Pr)_2$ in CH_3CN at 80 °C did not

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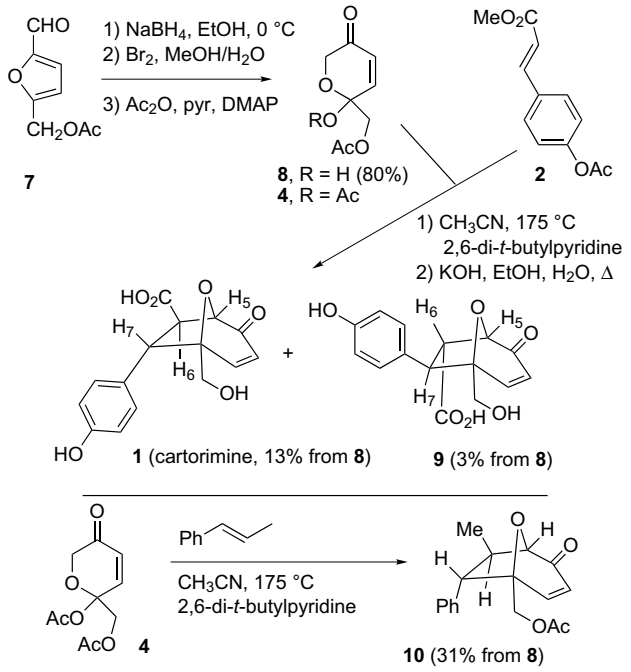

Scheme 3. Synthesis of cartorimine.

afford the desired cycloadduct. Thermal reaction in CH_3CN in a sealed tube at 150–175 °C was more successful, but not completely reproducible. Eventually, we concluded that residual pyridine from the preparation of **4** was important for the success of the reaction. Heating a 0.2 M solution of crude **4** in CH_3CN with 6 equiv of **2** and 1 equiv of 2,6-di-*t*-butylpyridine in a 175 °C oil bath for 14 h afforded the crude bis acetoxy methyl ester of **1**. Hydrolysis with KOH in 4:1 EtOH/H_2O at reflux for 20 h and preparative TLC afforded 16% (from **8**) of a 4:1 mixture of cartorimine (**1**) and the stereoisomer **9**, which were separated by reverse phase HPLC.[9] A similar reaction using pyridine, instead of 2,6-di-*t*-butylpyridine, afforded only 4% of a 3:1 mixture of **1** and **9**. The analogous cycloaddition of **4** with *trans*-β-methylstyrene provided 31% (from **8**) of **10**[10] regio- and stereospecifically, indicating that the electron-withdrawing carbomethoxy group of **2** retards the reaction.

The spectral data of **1** are identical to those previously reported.[1] Small NOEs from the aromatic hydrogens to the hydroxymethyl group of both **1** and **9** established that the minor product is a stereo- rather than a regioisomer. The vicinal coupling constants support this assignment. $J_{H5,H6}$ = 1.5 Hz in **1** and 7.9 Hz in **9**, while $J_{H6,H7}$ = 7.5 Hz in **1** and 4.3 Hz in **9**. These coupling constants are consistent with those expected from MM2 calculations and analogous to those in the related stereoisomeric adducts formed from oxypyrylium zwitterions and dimethyl fumarate.[6]

In conclusion, we have completed the first synthesis of cartorimine (**1**) using a possibly biomimetic [5+2] cycloaddition to efficiently construct the fully functionalized 8-oxabicyclo[3.2.1]octenone skeleton.

Acknowledgements

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References and notes

1. Yin, H.-B.; He, Z.-S.; Ye, Y. *J. Nat. Prod.* **2000**, *63*, 1164–1165. The ^{1}H NMR data[1] were referenced to CD_2HOD at δ 3.50 rather than δ 3.31. Private communication from Prof. Ye, September 10, 2004.
2. Lichtenthaler, F. W.; Brust, A.; Cuny, E. *Green Chem.* **2001**, *3*, 201–209.
3. (a) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359–3361; (b) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3361–3363.
4. (a) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1056–1057; (b) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1261–1265; (c) Sammes, P. G.; Street, L. J.; Kirby, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2729–2734; (d) Sammes, P. G.; Street, L. J. *J. Chem. Res. Synop.* **1984**, 196–197; (e) Sammes, P. G. *Gazz. Chim. Ital.* **1986**, *116*, 109–114.
5. Marshall, K. A.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9135–9145.
6. (a) Ohmori, N.; Miyazaki, T.; Kojima, S.; Ohkata, K. *Chem. Lett.* **2001**, 906–907; (b) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755–767.
7. For a review see: Ohkata, K.; Akiba, K.-Y. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1996; Vol. 65, pp 354–364.
8. Kuo, Y.-H.; Shih, K.-S. *Heterocycles* **1990**, *31*, 1941–1949.
9. 2,6-Di-*tert*-butylpyridine (0.45 mL, 2.01 mmol) was added to a solution of crude **4** (459 mg, 2.01 mmol) and **2** (2.664 g, 12.1 mmol, 6 equiv) in dry CH_3CN in a Schlenk vacuum tube with PTFE valve (10 mL). The resulting solution was degassed using the freeze–thaw method and heated in a 175 °C oil bath for 14 h. The reaction was cooled and concentrated to give 3.119 g of a black solid. Most of the unreacted **2** was removed by filtration through 50 g of silica gel (3:2 hexanes/EtOAc) to afford 239 mg of crude bis acetoxy ester, which was dissolved in 4:1 EtOH/H_2O (50 mL). KOH (178 mg, 3.18 mmol) was added and the resulting red solution was heated at reflux for 20 h and cooled. The solution was acidified to pH 3 using saturated NaH_2PO_4 solution and concentrated to remove EtOH. The resulting aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL) to remove less polar impurities. The resulting aqueous solution was saturated with NaCl and extracted with EtOAc (4 × 50 mL). The EtOAc solution was dried ($MgSO_4$) and concentrated to give 159 mg of crude **1**. PTLC (7:3 $CHCl_3$/acetone) gave 110 mg (16% from **2**) of a 4:1 mixture of **1** and **9**, which were separated by HPLC on a Zorbex Eclipse XDB-C18 4.6 × 250 mm column, 9:1 H_2O/MeOH, flow rate = 1 mL/min with 0.5 mg of sample: t_R = 12.3 (**9**), t_R = 18.3 (**1**). Data for **1**: ^{1}H NMR (CD_3OD) 7.07 (d, 2, J = 8.5), 6.80 (d, 1, J = 10.4), 6.71 (d, 2, J = 8.5), 6.18 (br d, 1, J = 10.4), 4.70 (br s, 1), 3.84 (d, 1, J = 6.7), 3.82 (d, 1, J = 12.5), 3.73 (d, 1, J = 12.5), 3.13 (br d, 1, J = 6.7); ^{13}C NMR (CD_3OD) 197.9, 158.2, 155.6, 131.1 (2 C), 128.9, 128.4, 116.4 (2 C), 88.4, 86.1, 64.2, 54.2 (2 C) (one quaternary C not observed). Data for **9**: ^{1}H NMR (CD_3OD) 7.47 (d, 1, J = 9.5), 7.09 (d, 2, J = 7.6), 6.73 (d, 2, J = 7.6), 6.05 (d, 1, J = 9.5), 3.83–3.64 (m, 2), 3.19 (d, 1, J = 12.2) (one H is under the OH peak at δ 4.8 and one H is under the MeOH peak at δ 3.31); ^{1}H NMR ((CD_3)$_2$CO)

7.57 (d, 1, J = 10.1), 7.15 (d, 2, J = 8.5), 6.81 (d, 2, J = 8.5), 6.01 (br d, 1, J = 10.1), 4.89 (br d, 1, J = 7.9), 3.83–3.79 (m, 1), 3.77 (d, 1, J = 4.3), 3.37 (d, 1, J = 11.6), 3.26 (d, 1, J = 11.6); ^{13}C NMR (CD_3OD) 157.8, 156.8, 132.1, 131.2 (2 C), 127.8, 116.3 (2 C), 88.7, 85.2, 65.5 (four C not observed).

10. Data for **10**: ^{1}H NMR ($CDCl_3$) 7.32–7.26 (m, 3), 7.14 (dd, 2, J = 7.0, 1.8), 6.70 (d, 1, J = 9.8), 6.26 (d, 1, J = 9.8), 4.46 (d, 1, J = 11.9), 4.27 (br s, 1), 4.21 (d, 1, J = 11.9), 3.00 (d, 1, J = 6.7), 2.54 (br dq, 1, J = 6.7, 6.7), 1.36 (d, 3, J = 6.7); ^{13}C NMR ($CDCl_3$) 195.8, 170.6, 151.1, 135.6, 128.9 (2 C), 128.7 (2 C), 128.3, 127.9, 88.0, 84.7, 65.3, 59.4, 43.0, 20.7, 19.6.