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Formal synthesis of (−)-morphine from D-glucal based on the cascade Claisen rearrangement

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Abstract—The formal synthesis of (−)-morphine is described. The C-ring in morphine was prepared in an optically pure form from D-glucal using Ferrier's carbocyclization reaction, and the vicinal tertiary and quaternary stereocenters in the C-ring were stereoselectively generated in a one-step reaction based on the cascade sequential Claisen rearrangement of an allylic vicinal diol derivative. After the one-step formation of the dibenzofuran structure, the intramolecular Friedel–Crafts type reaction effectively constructed the ABCE-phenanthrofuran skeleton. Introduction of a tosylamide function, followed by reductive cyclization furnished (−)-dihydroisocodeine, the known synthetic intermediate for (−)-morphine.

(−)-Morphine **1** is a well-known principal alkaloid isolated from opium poppy, *Papaver Somniferum*, and a number of structurally related alkaloids, such as (−)-codeine and (−)-thebaine, have also been discovered in the same plant.[1] Due to its significant effectiveness as an analgesic, morphine has been used as a medicine for a long time in spite of its serious addictive side effects. Its important biological activity as well as its highly challenging structure, a strained pentacyclic core with five contiguous chiral centers including a benzylic quaternary carbon (morphinan skeleton), has naturally received considerable attention from the synthetic community, and a number of synthetic studies and total syntheses have been reported.[2] In this Letter, we disclose a new and stereoselective synthesis of (−)-dihydroisocodeine **2**, the key intermediate of (−)-morphine,[2c] starting from D-glucal, in which the vicinal tertiary and quaternary carbons in the C-ring were stereoselectively generated in a one-step reaction by the cascade Claisen rearrangement.

Recently, we reported the total synthesis of (+)-galanthamine, an alkaloid possessing the same tricyclic dibenzofuran core as (−)-morphine, and revealed that the 2-nitrophenol-catalyzed Johnson–Claisen rearrangement of a cyclohexenol possessing a substituted phenyl group prepared from D-glucose by way of the Ferrier's carbocyclization as the key transformation is effective for the stereoselective generation of a benzylic quaternary carbon.[3] It was also shown that the dibenzofuran skeleton could be easily constructed by the intramolecular dealkylating etherification of a cyclohexene bearing a methoxyphenyl group. These successful results led us to apply a similar methodology to the synthesis of (−)-morphine **1** starting from carbohydrates. Our retrosynthetic analysis (Fig. 1) suggested that (−)-dihydroisocodeine **2**, which is the known synthetic intermediate in Parker's synthesis of (−)-morphine,[2c] would be an appropriate target compound. The formation of the morphinan skeleton in **2** was planned by the reductive cyclization of tosylamide **3** reported by Parker.[2c] The tetracyclic ring system in **3** was envisioned to be prepared by the intramolecular Friedel–Crafts type cyclization[2e,4] of aryl-aldehyde **4**, whose dibenzofuran structure was expected to be constructed by the epoxide-mediated intramolecular dealkylating etherification[2f,g] of cyclohexene **5** possessing a phenolic ether function. For the stereoselective construction of the vicinal tertiary and quaternary carbons in **5**, the cascade sequential Claisen rearrangement of cyclohexene-diol **6** was planned. If the cascade reaction works as expected (**6**→**5′**→**5**), the adjacent tertiary and quaternary carbons could be constructed in a one-step reaction, and the two C–O stereochemistries in the starting material **6** would

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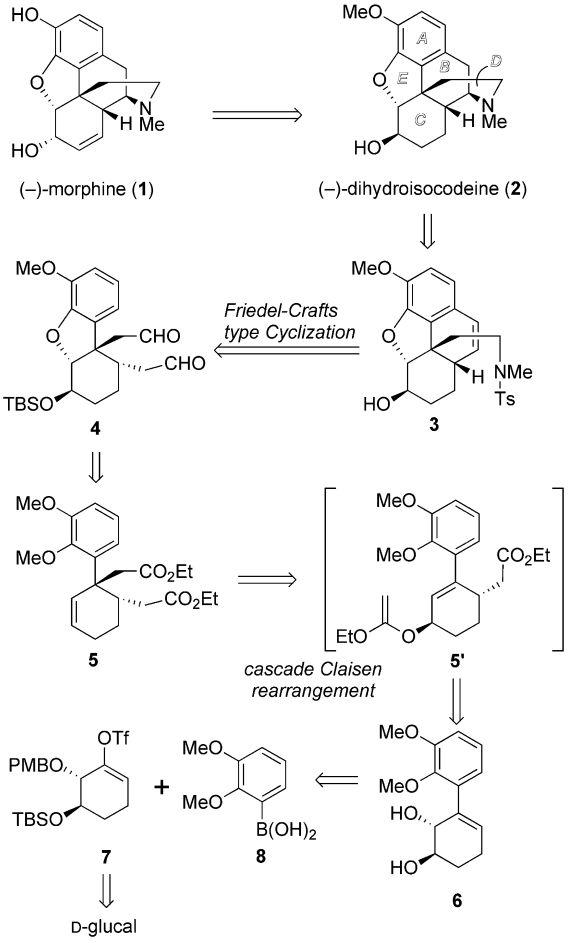
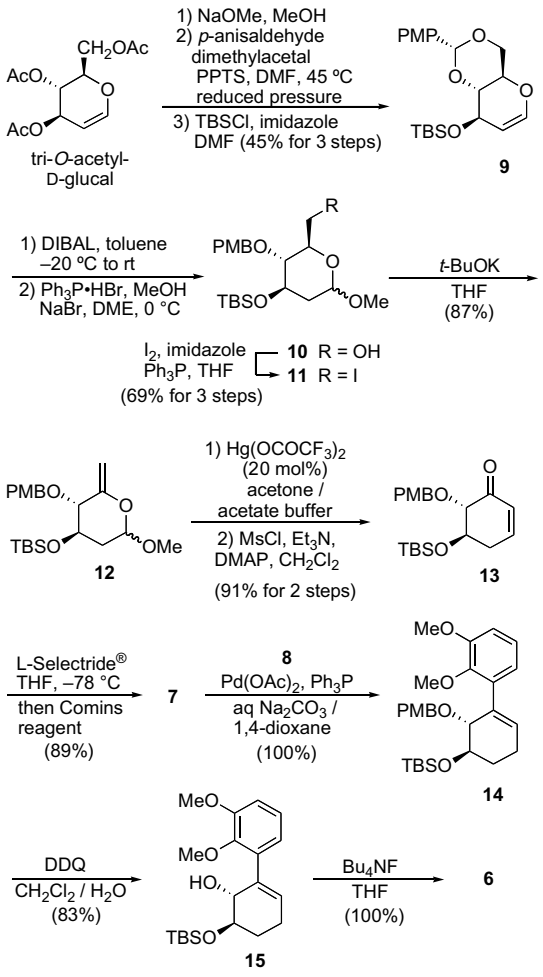


Figure 1. Structure of morphine and its retrosynthetic analysis. TBS = –$SiMe_2$(*t*-Bu), Tf = –SO_2CF_3, PMB = –$CH_2C_6H_4$(*p*-OMe).

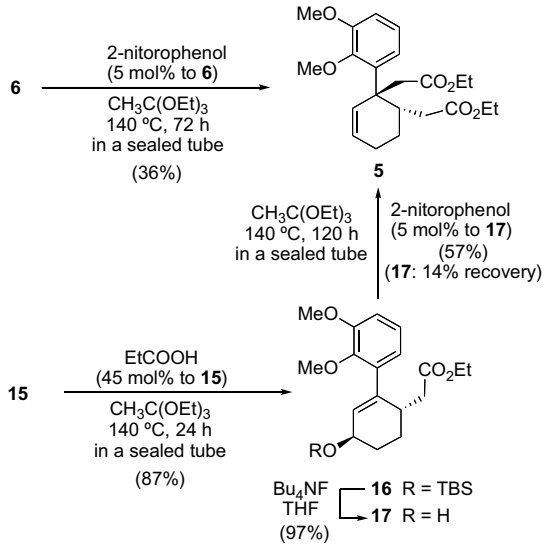


Scheme 1. PMP = –C_6H_4(*p*-OMe), L-Selectride® = Li[$CH(CH_3)$-CH_2CH_3]$_3$BH.

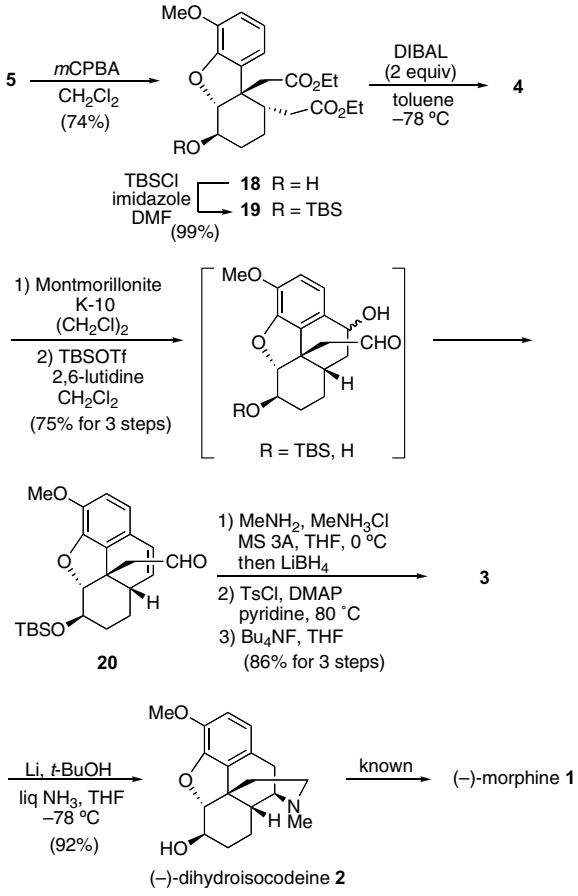
be effectively transferred to the C–C stereogenic centers in **5** by the sequential chirality transfer. Although a number of examples of the stereoselective C–C bond formation via chirality transfer utilizing the Claisen rearrangement have been reported,[5] its cascade versions have received little attention.[6] The cyclohexene-diol **6**, in turn, was envisioned to be prepared by the Suzuki–Miyaura coupling of vinyl triflate **7** with arylboronic acid **8**. The planned formation of the cyclohexene ring in **7** was to be prepared in optically active form starting from D-glucal utilizing Ferrier's carbocyclization reaction.[7]

The treatment of D-glucal, prepared from the commercially available tri-*O*-acetyl-D-glucal by de-*O*-acetylation, with *p*-anisaldehyde dimethylacetal produced a 4,6-*O*-anisylidene derivative, whose hydroxy group was protected as a TBS ether to afford the known **9**[8] in 45% overall yield (Scheme 1). Cleavage of the anisylidene acetal in **9** with DIBAL gave a primary alcohol derivative, which was transformed into methyl glycoside **10** by the action of methanol in the presence of Ph_3P·HBr.[9] The primary hydroxy group in **10** was replaced with iodide to give **11**[10] in 69% overall yield from **9**. The treatment of **11** with *t*-BuOK provided 5-enopyranoside **12** in 87% yield. Catalytic Ferrier's carbocyclization reaction[7c] of **12** in acetone–acetate buffer and subsequent β-elimination of the hydroxy function cleanly generated cyclohexenone **13** in 91% yield. The 1,4-reduction of **13** with L-Selectride®, followed by trapping of the resulting enolate with Comins reagent[11] provided the vinyl triflate **7** in 89% yield. Suzuki–Miyaura coupling[12] of **7** with 2,3-dimethoxyphenylboronic acid **8** smoothly proceeded at room temperature to quantitatively give **14**. Deprotection of the PMB group in **14** by the action of DDQ produced allylic alcohol **15** (83% yield). Removal of the *O*-TBS group in **15** provided the precursor of the cascade Claisen rearrangement, the vicinal allylic–homoallylic diol **6**,[13] in quantitative yield.

With the desired diol **6** in hand, the crucial step, the cascade sequential Claisen rearrangement was then explored (Scheme 2). After several attempts, it was found that when **6** was heated at 140 °C in triethyl orthoacetate in the presence of 2-nitrophenol in a sealed tube, the cascade Johnson–Claisen rearrangement successfully took place to provide the doubly rearranged product **5**[13] in moderate (36%) yield.[14] It is important to note that the vicinal tertiary and quaternary carbons in morphine were stereoselectively constructed in a



Scheme 2.



Scheme 3. *m*CPBA = *m*-chloroperbenzoic acid.

one-step reaction by this cascade rearrangement. On the other hand, the stepwise version was also investigated. Claisen rearrangement of allylic alcohol **15** in triethyl orthoacetate in the presence of propionic acid at 140 °C in a sealed tube for 24 h gave the rearranged product **16** in 87% yield.[15] After removal of the *O*-TBS group (97% yield), the resulting allylic alcohol **17** was heated in triethyl orthoacetate in the presence of 2-nitrophenol at 140 °C to provide **5** in 57% yield along with the recovery of **17** (14%). Thus, the stepwise approach provided the rearranged product **5** in 48% overall yield (56% overall yield based on the recovered starting material) from **15**.[16]

Having established the preparation of diester **5** by way of the cascade or stepwise Claisen rearrangement, we next turned our attention to the transformation of **5** into dihydroisocodeine **2** (Scheme 3). The reaction of **5** with *m*CPBA induced the intramolecular dealkylating etherification via an epoxide intermediate[2g] to give hydroxydibenzofuran derivative **18** in 74% yield in one-step. Other possible products, such as an α-epoxide or lactones, could not be isolated in this reaction.[17] The hydroxy group in **18** was protected as a TBS ether to give **19** in 99% yield. The reduction of **19** with DIBAL (2 equiv) at −78 °C afforded dialdehyde **4**, which was then treated with Montmorillonite K-10 in 1,2-dichloroethane at room temperature. Under these acidic conditions, the Friedel–Crafts type cyclization[18] took place, and subsequent dehydration of the resulting benzylic hydroxy group gave a mixture (ca. 1:1) of phenanthrofuran **20**[13] and its de-*O*-TBS derivative. After O-silylation of the mixture, tetracyclic aldehyde **20** was obtained in 75% yield from **19**. It is noteworthy that the cyclization/dehydration process proceeded in a high yield under relatively mild reaction conditions.[19] The reductive amination of **20**, followed by N-tosylation and de-O-silylation afforded tosylamide **3**, which is known as the intermediate for the synthesis of morphine reported by Parker[2c] in 86% yield. Finally, the treatment of **3** with Li in liq. NH_3 in the presence of *t*-BuOH[2c] cleanly provided (−)-dihydroisocodeine **2**[13] in 92% yield. The ^1H and ^{13}C NMR data of **2** were totally identical to those reported by Parker,[2c] and the $[\alpha]_D$ value of the synthetic compound $\{[\alpha]_D^{28}$ −132 (*c* 0.32, $CHCl_3$)} showed good accordance with those reported by Ginsburg[20] $\{[\alpha]_D^{28}$ −136 (*c* 2.55, $CHCl_3$)}.

In summary, a new synthetic route to (−)-dihydroisocodeine **2** starting from D-glucal, representing the formal synthesis of (−)-morphine **1** has been established. This stereoselective synthesis demonstrated that the cascade Claisen rearrangement is highly effective for the stereoselective one-step construction of the vicinal tertiary and quaternary carbons. This novel method, that is, the cascade sigmatropic rearrangement of allylic vicinal diols, would be applicable to the synthesis of a variety of natural products. It is also shown that the combination of the intramolecular dealkylating etherfication via an epoxide intermediate and the Friedel–Crafts type cyclization of the aryl-aldehyde are useful for the construction of the ABCE-tetracyclic skeleton of morphinan alkaloids.

Acknowledgements

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21st Century COE program 'KEIO LCC') for financial assistance.

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13. *Data of* **6**: white crystals; $[\alpha]_D^{24.5}$ −41 (*c* 0.87, $CHCl_3$); mp 110.5–111.5 °C; IR ν_{max} (KBr) 3350, 2930 and 1580 cm^{-1}; ^{1}H NMR δ 7.04 (dd, 1H, J = 12.0 and 12.0 Hz), 6.88 (d, 1H, J = 12.0 Hz), 6.80 (d, 1H, J = 12.0 Hz), 5.82 (ddd, 1H, J = 3.6, 3.6 and 1.8 Hz), 4.45 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.84 (m, 1H), 2.89 (d, 1H, J = 5.1 Hz), 2.59 (br, 1H), 2.30–2.36 (m, 2H), 2.08 (dddd, 1H, J = 12.9, 4.5, 4.5 and 4.2 Hz), 1.81 (m, 1H); ^{13}C NMR δ 152.5, 145.6, 137.7, 134.3, 128.5, 124.7, 122.4, 111.5, 74.5, 72.2, 60.9, 55.8, 27.4, 24.5; LRMS (EI) *m*/*z* 250 (M^+, 29), 232 (83), 214 (100), 199 (64), 184 (43), 159 (39); HRMS (EI) *m*/*z* 250.1205, calcd for $C_{14}H_{18}O_4$, M^+, 250.1205. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.28; H, 7.14. *Data of* **5**: syrup; $[\alpha]_D^{27}$ −54 (*c* 0.61, $CHCl_3$); IR ν_{max} (neat) 2940 and 1730 cm^{-1}; ^{1}H NMR δ 6.94 (dd, 1H, J = 8.1 and 8.1 Hz), 6.85 (dd, 1H, J = 8.1 and 2.1 Hz), 6.83 (dd, 1H, J = 8.1 and 2.1 Hz), 6.13 (d, 1H, J = 10.5 Hz), 5.85 (ddd, 1H, J = 10.5, 3.3 and 3.3 Hz), 4.03 (q, 2H, J = 7.2 Hz), 3.92 (q, 2H, J = 7.2 Hz), 3.89 (s, 3H), 3.84 (s, 3H), 3.64 (d, 1H, J = 15.0 Hz), 2.89 (d, 1H, J = 15.0 Hz), 2.73 (dddd, 1H, J = 12.0, 5.4, 3.3 and 3.3 Hz), 2.09 (dd, 1H, J = 15.3 and 3.3 Hz), 1.91 (dd, 1H, J = 15.3 and 12.0 Hz), 1.77–2.18 (m, 3H), 1.53 (dddd, 1H, J = 14.1, 5.4, 5.4 and 5.4 Hz), 1.18 (t, 3H, J = 7.2 Hz), 1.02 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 173.6, 171.8, 152.8, 148.1, 135.8, 132.5, 126.1, 122.6, 122.3, 111.38, 60.3, 60.0, 59.7, 55.7, 45.3, 44.6, 37.8, 35.3, 21.9, 21.2, 14.2, 14.0; HRMS (FAB) *m*/*z* 413.1932, calcd for $C_{22}H_{30}NaO_6$, $(M+Na)^+$, 413.1940. *Data of* **20**: syrup; $[\alpha]_D^{24}$ +21 (*c* 0.54, $CHCl_3$); IR ν_{max} (neat) 2920, 2860, 1720 and 1500 cm^{-1}; ^{1}H NMR δ 9.55 (dd, 1H, J = 2.5 and 2.2 Hz), 6.74 (d, 1H, J = 8.0 Hz), 6.66 (d, 1H, J = 8.0 Hz), 6.42 (dd, 1H, J = 9.5 and0.8 Hz), 5.81 (dd, 1H, J = 9.5 and 5.9 Hz), 4.61 (d, 1H, J = 7.1 Hz), 3.90 (s, 3H), 3.43 (ddd, 1H, J = 11.9, 7.1 and 4.6 Hz), 2.64 (dd, 1H, J = 15.6 and 2.2 Hz), 2.52 (dd, 1H, J = 15.6 and 2.5 Hz), 2.51 (dddd, 1H, J = 11.5, 5.9, 4.4 and 0.8 Hz), 1.80 (dddd, 1H, J = 13.7, 4.7, 4.4 and 2.5 Hz), 1.58 (m, 1H), 1.38 (dddd, 1H, J = 13.7, 13.4, 11.9 and 2.5 Hz), 0.85–1.01 (m, 1H), 0.96 (s, 9H), 0.12 (s, 3H), 0.03 (s, 3H); ^{13}C NMR δ 201.2, 145.5, 144.7, 130.0, 127.9, 123.7, 123.3, 117.9, 114.3, 97.6, 73.6, 56.8, 50.3, 44.8, 39.4, 29.6, 26.9, 25.8, 18.1, −4.6, −5.0; LRMS (EI) *m*/*z* 400 (M^+, 30), 356 (27), 343 (56), 299 (100). HRMS (EI) *m*/*z* 400.2074, calcd For $C_{23}H_{32}O_4Si$, M^+, 400.2070. *Data of* **2**: white crystals; mp 201–202 °C; $[\alpha]_D^{28}$ −132 (*c* 0.32, $CHCl_3$) {lit.[18] mp 199–200 °C; $[\alpha]_D^{28}$ −136 (*c* 2.55, $CHCl_3$)}; IR ν_{max} (neat) 3400, 2920, 2860, 1640, 1620 and 1500 cm^{-1}; ^{1}H NMR δ 6.73 (d, 1H, J = 8.3 Hz), 6.65 (d, 1H, J = 8.3 Hz), 4.38 (d, 1H, J = 6.6 Hz), 3.87 (s, 3H), 3.44 (ddd, 1H, J = 12.4, 6.6 and 4.9 Hz), 3.28 (br s, 1H), 3.02 (d, 1H, J = 18.5 Hz), 2.70 (dd, 1H, J = 12.2 and 4.1 Hz), 2.52 (s, 1H), 2.49 (dd, 1H, J = 18.5 and 5.1 Hz), 2.40 (br d, 1H, J = 12.9 Hz), 2.28 (ddd, 1H, J = 12.4, 12.4 and 3.9 Hz), 2.01 (ddd, 1H, J = 12.4, 12.4 and 4.1 Hz), 1.82 (dddd, 1H, J = 12.9, 4.9, 2.7 and 2.7 Hz), 1.74 (dd, 1H, J = 12.4 and 3.9 Hz), 1.61 (dddd, 1H, J = 12.9, 2.7, 2.7 and 2.7 Hz), 1.39 (dddd, 1H, J = 12.9, 12.9, 12.4 and 2.7 Hz), 0.97 (dddd, 1H, J = 12.9, 12.9, 12.9 and 2.7 Hz); ^{13}C NMR δ 144.2, 143.9, 129.9, 125.2, 119.1, 113.8, 96.9, 73.1, 59.9, 56.5, 47.2, 42.8, 42.4, 41.8, 34.7, 29.8, 23.5, 20.5; LRMS (EI) *m*/*z* 301 (M^+, 100), 286 (1). HRMS (EI) *m*/*z* 301.1677. Calcd For $C_{18}H_{23}NO_3$, M^+, 301.1678.
14. Attempted Eschenmoser–Claisen rearrangement (*N*,*N*-dimethylacetamide dimethylacetal, toluene, reflux) and Ireland–Claisen rearrangement {(1) Ac_2O, pyridine (2) LHMDS then $TMSCl/Et_3N$} of **6** produced no cascade rearranged products.
15. When the Claisen rearrangement was carried out in the presence of 2-nitorophenol (53 mol %), the rearranged product was obtained in a less satisfactory yield (53%).
16. The moderate yields of the cascade rearrangement and the second rearrangement of the stepwise version were mainly due to the decomposition of the substrates. The decomposition would be induced by the formation of stabilized conjugated carbocations generated from cyclohexenol derivatives **6**, **17** and/or **5′** by elimination of water or ethyl acetate under the acidic reaction conditions. For the acid sensitivity of the structurally related cyclohexenol, see: Chida, N.; Sugihara, K.; Amano, S.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 275–280.

17. Although the exact reasons for the observed stereoselectivity in the epoxidation of **5** have not been clear so far, it may be reasonable to suppose that the steric factor (steric hindrance caused by the presence of an α-aromatic ring and an α-ethoxycarbonylmethyl group) as well as the stereoelectronic effects associated with an α-dimethoxyphenyl group would be responsible for the stereoselective formation of a β-epoxide. As a possible stereoelectronic effect, the concepts of the Cieplak postulate might be extended to explain the observed π-facial selectivity. In the transition state for epoxidation of **5** by the β-attack of *m*CPBA, the vacant orbitals ($\sigma^*_{\neq}$) that develop in the α-face along with formation of the incipient C–O bonds may interact with n-electrons on the *o*-methoxy group (n_o) in the α-aromatic ring. These through-space stabilizing interactions (remote n_o–$\sigma^*_{\neq}$ interactions) would lead to form the β-epoxide intermediate. For reviews of stereoelectronic effects in π-facial selectivities, see (a) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265–1336; (b) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337–1375.
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