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Intramolecular ene reaction on a bicyclo[3.2.1]octane system: an alternative route to (−)-kainic acid

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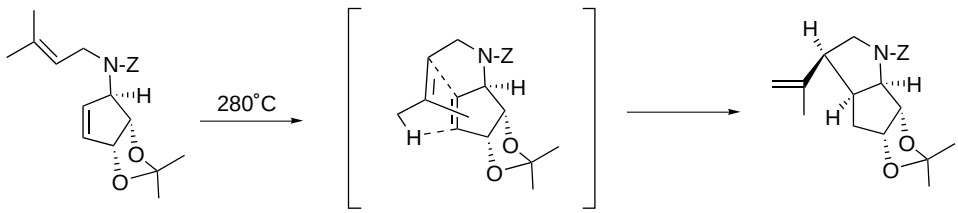
Abstract—The intramolecular ene reaction of the 1,6-diene on a bicyclo[3.2.1]octane framework proceeds in a highly diastereoselective manner to form a trisubstituted pyrrolidine on the pyran ring in excellent yield. Its stereochemistry has been determined unambiguously by converting it into the known compound serving as a key intermediate of (−)-kainic acid.

We have observed that a regio- and diastereoselective ring formation occurred on a cyclopentane ring to give the product **3** bearing a *cis*-2,3,4-trisubstituted pyrrolidine system by an intramolecular ene reaction when the 1,6-diene **1** was heated in diphenyl ether[1] (Scheme 1). In this instance, the diastereoselectivity observed is explained by the intervention of a rigid transition state **2** that placed the ene component most appropriately on the enophile cyclopentene for the intramolecular ene reaction to proceed.[2] We are, therefore, very interested in the same reaction of the 1,6-diene **4** carrying the ene component on the enophile having a half-chair six-membered ring, which has to take a less stable half-boat configuration **5a** to initiate the intramolecular ene reaction to give rise to the product **6** having the same stereochemistry as the five-membered counterpart **3**. Moreover, our further interest is in the generation of a pyrrolidine diastereomer **7** having a *trans*-3,4-stereochemistry through an alternative transition state **5b** owing to the more flexible six-membered framework if the intramolecular ene reaction proceeds (Scheme 2).

The intramolecular ene reaction occurred cleanly to give a single product supporting the structure either **6** or **7** in nearly quantitative yield when the 1,6-diene **4**, prepared from enantiopure enone (+)-**8** having a dioxabicyclo[3.2.1]octane framework, was refluxed in diphenyl ether under the same conditions as for **1**. However, the structure of the ene product could not be determined at this point on the basis of its spectroscopic data. To determine the structure as well as to utilize the excellent result, we examined its conversion into *N*-carbobenzoxy-2-carbomethoxy-3-methylcarbomethoxy-4-isopropenylpyrrolidine since its *cis*-2,3,4 isomer was prepared from the ene product **3** and used as a key intermediate for the synthesis of a natural kainoid amino acid, (−)-kainic acid.[1,3]

Prior to the structure determination of the ene product, synthesis of the 1,6-diene **4** used in the ene reaction has to be described. Thus, (+)-enone[4] **8** (>99% ee), prepared from furfural by employing either a chemical[5] or enzymatic[6] chiral induction step, was transformed into



1 **2** **3**

Z = CO_2Bn

Scheme 1.

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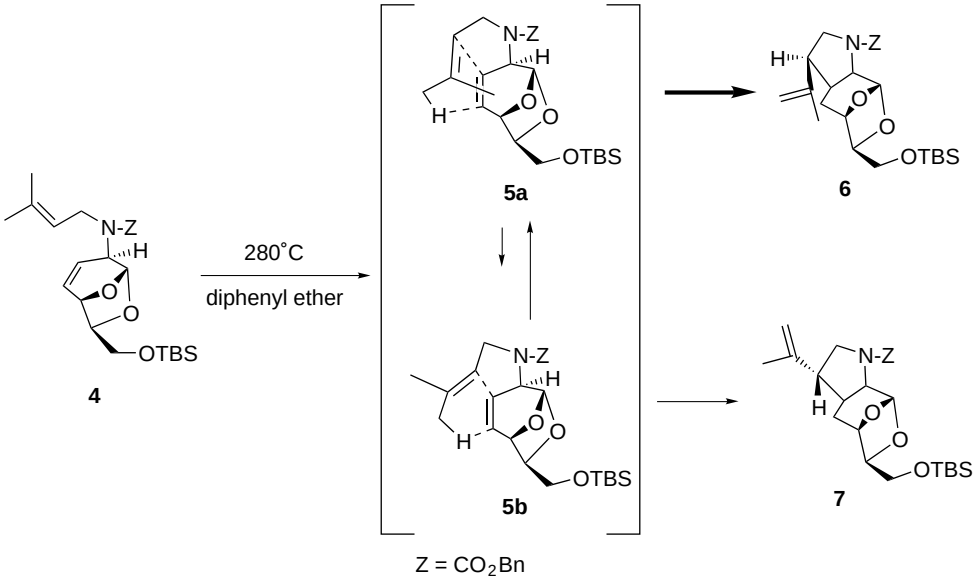
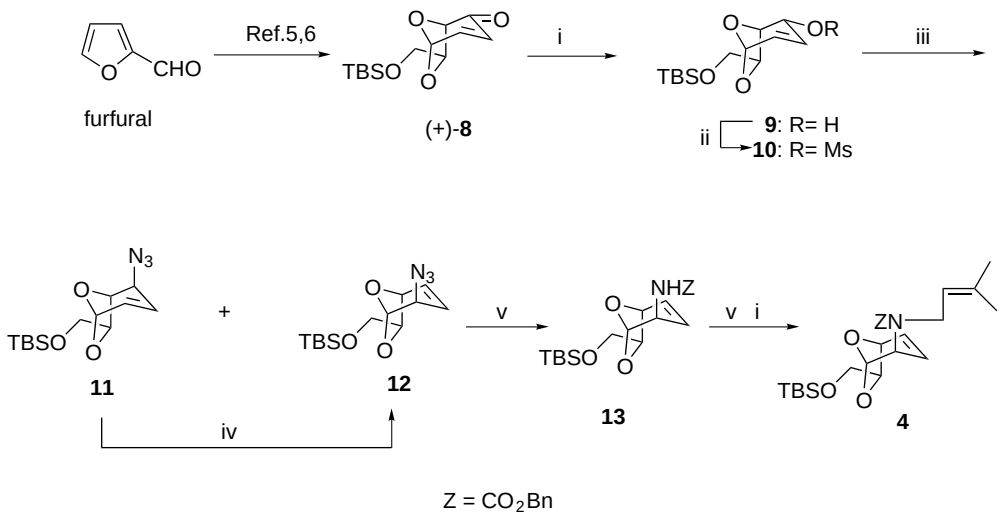


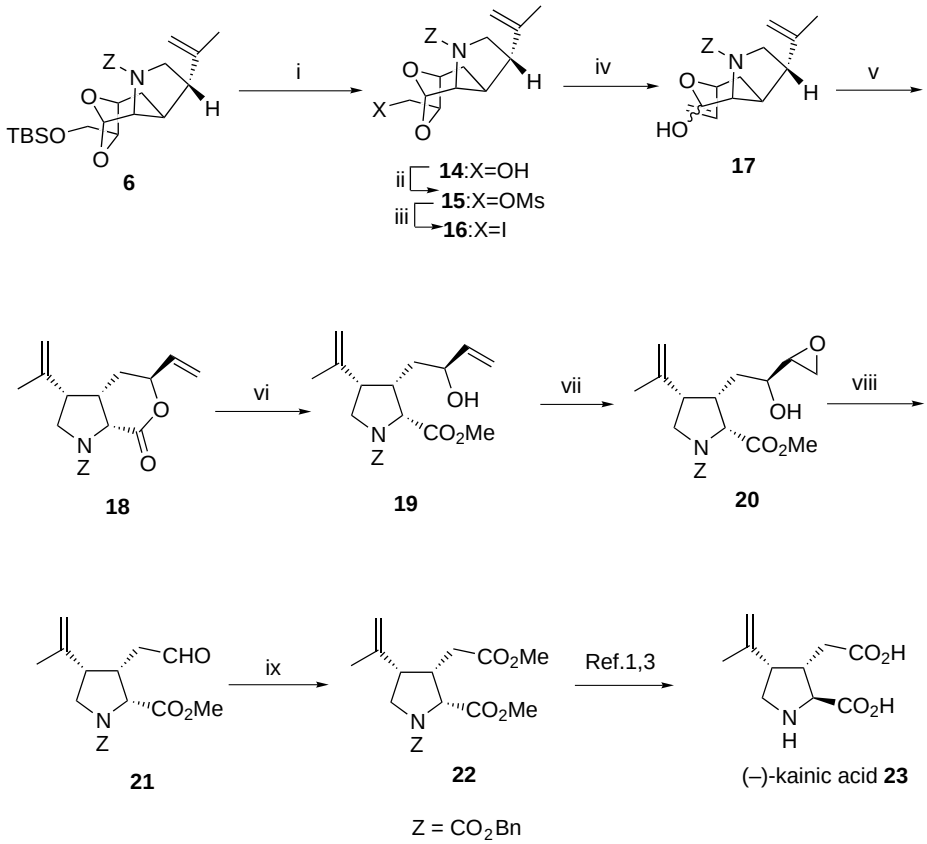
Scheme 2.

the *endo*-mesylate **10** via *endo*-alcohol **9**. The 1,2-reduction[7] of **8** proceeded diastereoselectively from the convex-face of the molecule to give **8** owing to its biased framework. Reaction of **10** with sodium azide in DMF proceeded in a competitive S_N2 and S_N2' pathway to furnish a readily separable mixture of two regioisomeric *exo*-azides, **11**: $[\alpha]_D^{30}$ +273.0 (*c* 0.7, $CHCl_3$), and **12**: $[\alpha]_D^{29}$ −236.5 (*c* 1.0, $CHCl_3$), in a ratio of 1:1.2 after silylation of some desilylated products in the same flask. Fortunately, after separation the undesired isomer **11** furnished an equilibrium mixture of **11** and **12** in a ratio of 1:2.4 on reflux in toluene for 6 h presumably through a [3,3]-sigmatropic pathway.[8] Total yield of **12** from the mixture was attainable up to 93% after repetition of the rearrangement sequence three times. Reduction of azide **12** with lithium aluminum hydride, followed by *N*-carbobenzoxylation afforded secondary carbamate **13**, $[\alpha]_D^{30}$ −89.8 (*c* 0.9, $CHCl_3$), which furnished the substrate 1,6-diene **4**, $[\alpha]_D^{29}$ −82.6 (*c* 1.0, $CHCl_3$), by *N*-alkylation with prenyl chloride under standard conditions. As mentioned, **4** furnished a single intramolecular ene product, $[\alpha]_D^{25}$ +25.5 (*c* 0.5, $CHCl_3$), in 98% yield on refluxed in diphenyl ether for 30 min in the presence of sodium hydrogen carbonate (Scheme 3).

The structure of the ene product was eventually determined as **6** having a *cis*-2,3,4 pyrrolidine structure, but not as **7** having a *trans*-2,3,4 stereochemistry by the following transformation. Thus, the ene product confirmed later as **6** was first desilylated to give primary alcohol **14**, $[\alpha]_D^{25}$ +6.6 (*c* 0.6, $CHCl_3$), which was further transformed into iodide **16**, $[\alpha]_D^{25}$ +50.8 (*c* 0.5, $CHCl_3$), via mesylate **15**. Refluxing **16** with zinc in methanol containing acetic acid induced reductive ring-opening to give vinyl-hemiacetal **17** as an epimeric mixture, which



Scheme 3. *Reagents and conditions*: (i) $NaBH_4$, $CeCl_3$–$7H_2O$, MeOH, −78°C (98%); (ii) MsCl, Et_3N, CH_2Cl_2; (iii) NaN_3, DMF, 80°C then TBS–Cl, imidazole (1:1.2 mixture, 89%, two steps); (iv) toluene, reflux, 6 h (1:2.4 mixture, 93%); (v) $LiAlH_4$, Et_2O, 0°C then Cl–CO_2Bn(Cl-Z), K_2CO_3, 0°C (98%, two steps); (vi) prenyl–Cl, NaH, DMF, 0°C (83%).



Scheme 4. *Reagents and conditions*: (i) TBAF, THF (97%); (ii) Ms–Cl, Et_3N, CH_2Cl_2; (iii) LiI, THF, reflux (98%, two steps); (iv) Zn, AcOH–MeOH (1:10), reflux (90%); (v) TPAP–NMO, CH_2Cl_2–MeCN (4:1) (83%); (vi) NaOMe (2 equiv.), MeOH, rt (75%, recovery 15%); (vii) Bu^tO_2H, $VO(acac)_2$, benzene, 40°C (78%); (viii) PhSH, NaH, THF, then aq. $NaIO_4$, 0°C (79%); (ix) $NaClO_2$–NH_2SO_3H, 50% aq. dioxane, then CH_2N_2, MeOH (63%).

was oxidized to give the single δ-lactone **18**, $[\alpha]_D^{28}$ +35.6 (*c* 0.5, $CHCl_3$). On being stirred with two equivalents of sodium methoxide in methanol, **18** underwent solvolysis reaction to give a 5:1 equilibrium mixture of methyl ester **19**, $[\alpha]_D^{28}$ +38.8 (*c* 0.3, $CHCl_3$), and starting lactone **18** which were separated in yields of 75 and 15%.

To discriminate two double bonds in the molecule, the ester **19** was treated with *tert*-butyl hydroperoxide in benzene in the presence of vanadyl acetylacetonate[9] at 40°C to give rise to glycidol **20**, $[\alpha]_D^{27}$ +44.0 (*c* 0.3, $CHCl_3$), as a single product without affection of the isopropenyl functionality. Having discriminated the two double bonds in the molecule, the epoxy functionality of **20** was cleaved with thiophenol in THF in the presence of sodium hydride to give 1,2-diol which, without separation, was immediately cleaved in the same flask with aqueous sodium periodate to furnish aldehyde **21**, $[\alpha]_D^{27}$ +25.8 (*c* 0.2, $CHCl_3$). Treatment of **21** with sodium chlorite-sulfamic acid[10] in aqueous dioxane allowed smooth oxidation of the formyl functionality to give dimethyl ester **22**, $[\alpha]_D^{28}$ +22.1 (*c* 0.2, $CHCl_3$), after esterification with diazomethane, which was identical in all respects with an authentic dimethyl ester[1] **22**, $[\alpha]_D^{25}$ +21.6 (*c* 0.2, $CHCl_3$), thus, proving the structure of the starting **6**. This also concluded that the stereochemical course of the ene reaction of **4** is consistent with transition state **5a** as in the five-membered counterpart **1**. At the same time, an alternative route to (−)-kainic acid **23** was established since it has been prepared in two steps[1,3] from the diester **22** (Scheme 4).

In conclusion, we have found the intramolecular ene reaction of the 1,6-diene on a bicyclo[3.2.1]octane framework proceeds in a highly diastereoselective manner to form a single trisubstituted pyrrolidine on the pyran ring in excellent yield. Its stereochemistry has been determined unambiguously by converting it into the known compound serving as a key intermediate of (−)-kainic acid.

Acknowledgements

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