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Stereocontrolled approach to acromelic acids

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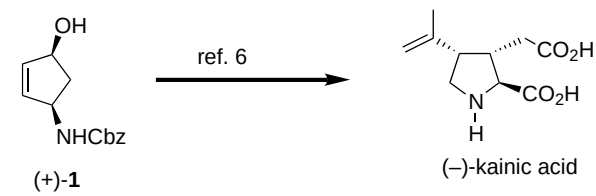
Abstract—A potential stereocontrolled route to acromelic acids, neuroexitatory amino acids isolated from the mushroom *Clitocybe acromelalga*, has been developed by employing either concurrent Chugaev-ene reaction or retro-Diels–Alder-ene reaction and regioselective pyridinecarboxylate formation reaction as the key steps.

Acromelic acids, members of the kainoid amino acid family,[1] have been isolated from the poisonous mushroom *Clitocycbe acromelalga* and are reported to exhibit much more potent neuroexitatory activity[2] than (−)-kainic acid, the 4-isopropenyl analogue of acromelic acids and the parent compound of the kainoid group, isolated from the marine algae *Digenea simplex*[3] (Fig. 1). Although several enantiocontrolled syntheses of acromelic acids have been reported so far,[4,5] all suffered from difficulty in the installation of an appropriately functionalized pyridine moiety on the C4 center of the common pyrrolidine framework. Quite recently, we developed an efficient diastereospecific construction of a *cis*-2,3,4-trisubstituted pyrrolidine leading to (−)-kainic acid from a chiral building block (+)-**1** by employing concurrent Chugaev-ene reaction as the key step[6] (Scheme 1).

In the present study, we explored synthesis of trisubstituted pyrrolidine carrying an appropriate functionality for the construction of the pyridinecarboxylate moiety on the C4-center by employing the same methodology so as to develop a new entry into the synthesis of acromelic acids. We report here a synthesis of two trisubstituted pyrrolidines carrying a pyridinecarboxylate moiety on the C4 center potentially utilizable for the synthesis of acromelic acids A, B, D and E.



Scheme 1.

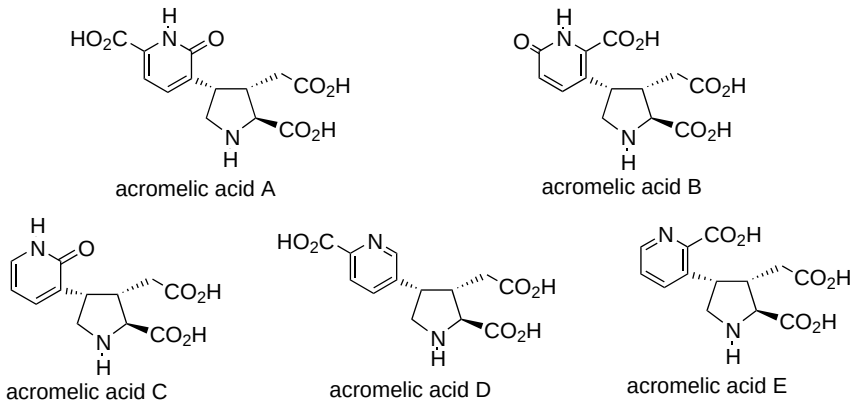


Figure 1.

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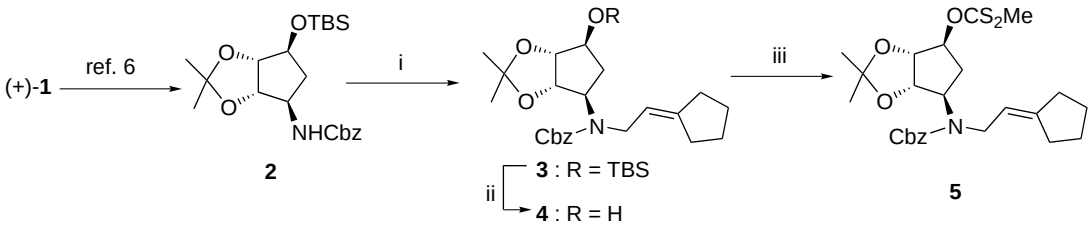
Thus, secondary carbamate **2**, obtained from enantiopure (+)-**1**, was transformed into the tertiary carbamate **3**, $[\alpha]_D^{30}$ −9.5 (*c* 0.4, $CHCl_3$), on reaction with cyclopentylidenethyl chloride[7] under standard conditions. After desilylation of **3**, the resulting alcohol **4**, $[\alpha]_D^{31}$ −16.4 (*c* 0.8, $CHCl_3$), was transformed into the xanthate **5**, $[\alpha]_D^{30}$ +27.1 (*c* 1.0, $CHCl_3$), used as the substrate for the key reaction (Scheme 2).

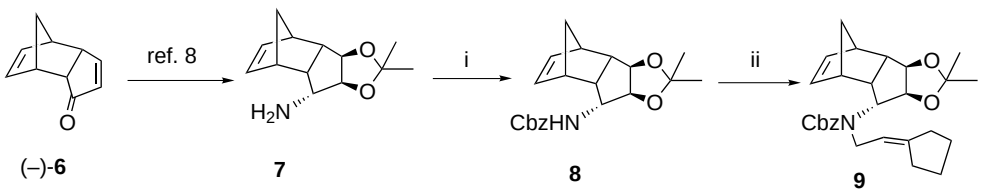
On the other hand, the known primary amine[8] **7**, obtained from enantiopure ketodicyclopentadiene[9] (KDP) (−)-**6**, was transformed into the tertiary carbamate **9**, $[\alpha]_D^{27}$ −49.6 (*c* 0.8, $CHCl_3$), via the secondary carbamate **8**, $[\alpha]_D^{27}$ −74.5 (*c* 0.9, $CHCl_3$), under standard conditions. Since **9** was expected to undergo retro-Diels–Alder-ene reaction under thermolysis conditions[10] to give rise to the same product as the product from the xanthate **5** through the same intermediate, we were very interested in the outcome of these two compounds under thermolysis conditions (Scheme 3).

After several experiments, it was found that both **5** and **9** furnished the same product **11** in good yields on reflux in diphenyl ether at 280°C. Namely, the xanthate **5** afforded **11**, $[\alpha]_D^{30}$ −28.0 (*c* 0.8, $CHCl_3$), diastereoselectively, in 89% yield after 45 min, while the KDP-derived carbamate **6** furnished the same product **11**, $[\alpha]_D^{27}$ −29.1 (*c* 0.9, $CHCl_3$), diastereoselectively, in 71% yield from **9** after 2 h. The difference in reaction rates between the two substrates may be due to the initial step where the Chugaev reaction seemed to proceed much faster than the retro-Diels–Alder reaction. At any rate, these results indicated that both **5** and **9** generated initially the same cyclopentene intermediate **10** which then underwent intramolecular ene reaction under the same conditions to yield the single trisubstituted pyrrolidine **11**. Since the product **11** is present as a mixture of rotamers, determination of its stereochemistry was not an easy task. However, NOESY NMR studies (500 MHz) at 60°C revealed three hydrogens on C2, C3 and C4 centers to be placed on the same face of the pyrrolidine ring as expected from our previous synthesis of (−)-kainic acid mentioned above[6] (Scheme 4).

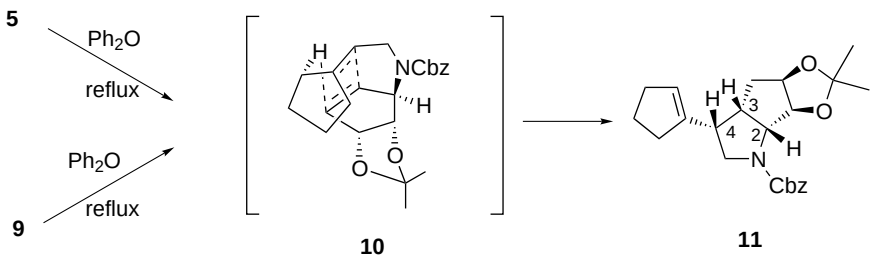
Construction of the pyridinecarboxylic acid moiety on the C4 center was next examined using the pyrrolidine **11** thus obtained. Hydroboration–oxidation of **11** afforded the secondary alcohol **12**, as a mixture of epimers, which was oxidized to the ketone **13**. Regioselective carbomethoxylation of **13** was accomplished under kinetic conditions using Mander's reagent[11] to give the β-keto ester **14** which was transformed into the α,β-unsaturated ester **16** by sequential chemoselective reduction using zinc borohydride[12] and regioselective dehydration via the alcohol **15**. Ozonolysis of **16**, followed by treatment of the crude product **17** with



Scheme 2. *Reagents and conditions*: (i) cyclopentylidenethyl chloride, NaH, NaI (cat.), THF (75%). (ii) TBAF, THF (95%). (iii) CS_2, NaH, MeI, THF, −30 to 0°C (98%).

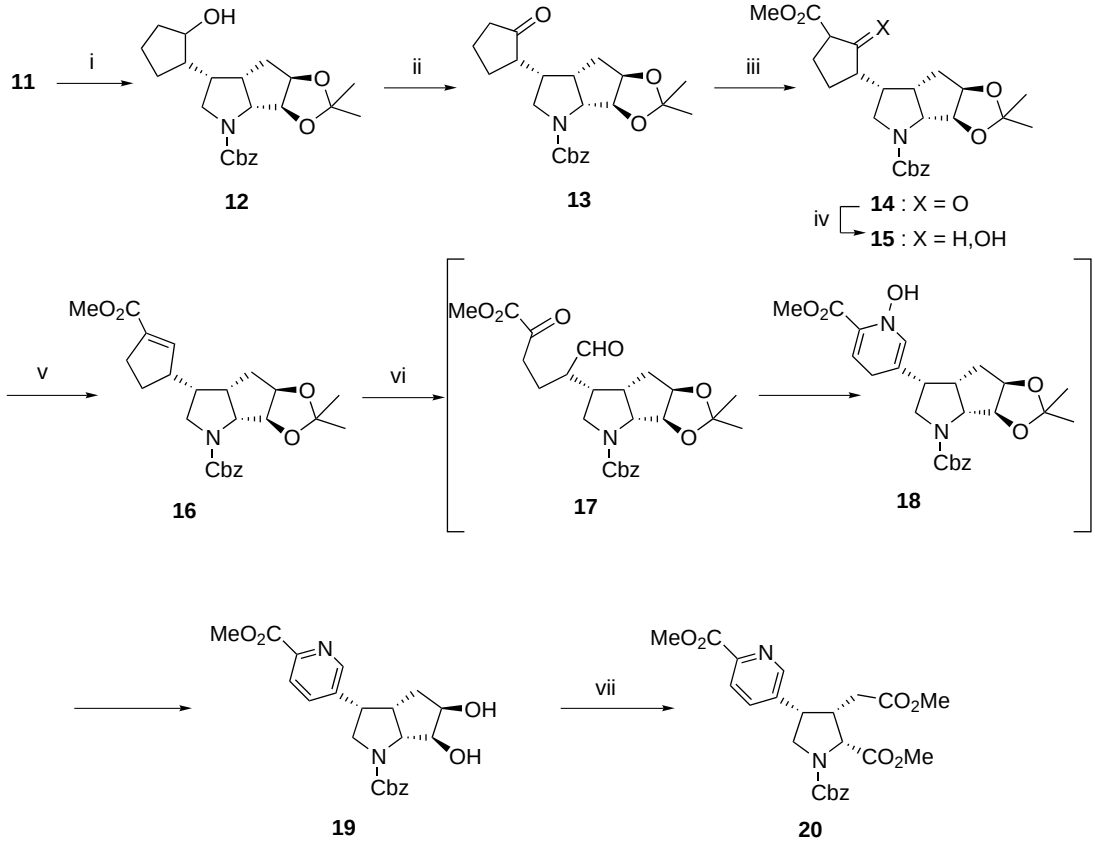


Scheme 3. *Reagents and conditions*: (i) Cbz-Cl, K_2CO_3, Et_2O (41% from **6**). (ii) cyclopentylidenethyl chloride, NaH, NaI (cat.), THF (71%).

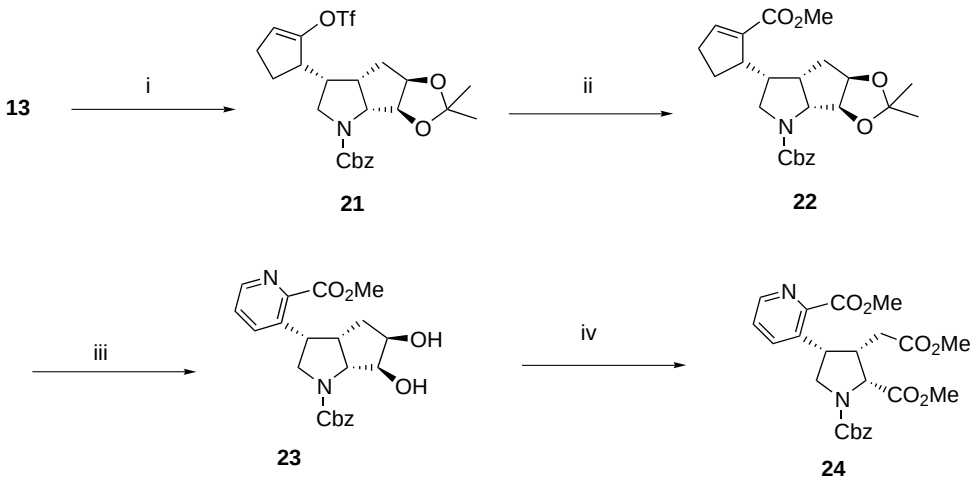


Scheme 4.

hydroxylamine hydrochloride[13] in methanol at reflux proceeded in the expected way to furnish the pyridine **19**, $[\alpha]_D^{25}$ −36.5 (*c* 0.8, $CHCl_3$), in one step with concurrent removal of the acetonide protection group under the conditions. The reaction may be presumed to proceed through a transient generation of *N*-hydroxy-1,4-dihydropyridine intermediate **18** followed by dehydration to give **19**. Conversion of **19** to the trimethyl ester **20**, $[\alpha]_D^{25}$ −7.4 (*c* 1.0, $CHCl_3$), the potential precursor for the synthesis of acromelic acids A and D, was carried out by sequential glycol cleavage and Jones oxidation followed by workup with diazomethane[6] (Scheme 5).



Scheme 5. *Reagents and conditions*: (i) BH_3-Me_2S, THF, 0°C, then 30% H_2O_2, 3N NaOH (89%). (ii) PCC, CH_2Cl_2 (90%). (iii) MeO_2CCN, LiHMDS, THF, −78°C (81%). (iv) $Zn(BH_4)_2$, Et_2O, 0°C. (v) Ms-Cl, Et_3N, CH_2Cl_2, then DBU, THF, reflux (50% from **14**). (vi) O_3, CH_2Cl_2, Me_2S, then NH_2OH-HCl, MeOH, reflux (61%). (vii) $NaIO_4$, aq. THF, 0°C, then Jones oxidation, 0°C, then CH_2N_2 (31%).



Scheme 6. *Reagents and conditions*: (i) 2-(*N*,*N*-trifrlyimino)pyridine, KHMDS, THF, −78°C (86%). (ii) Pd $(OAc)_2$, Et_3N, Ph_3P, CO, MeOH, DMF (92%). (iii) O_3, CH_2Cl_2, Me_2S, then NH_2OH-HCl, MeOH, reflux. (iv) $NaIO_4$, aq. THF, 0°C, then Jones oxidation, 0°C, then CH_2N_2 (26% for four steps).

The isomeric pyridinecarboxylate **24**, the potential precursor for the synthesis of acromelic acid B and E, was also prepared from the same key intermediate **11**. Thus, the ketone **13**, generated from **11**, was first transformed into the enol triflate **21**, regioselectively, using Comins' reagent[14] under kinetic conditions. Palladium-mediated carbomethoxylation[15] of **21** proceeded smoothly to afford the α,β-unsaturated ester **22** isomeric to the ester **16** above. Under the same conditions above involving ozonolysis and condensation with hydroxylamine hydrochloride, **22** furnished the pyridinecarboxylate **23** with concurrent removal of the acetonide protecting group as for the regioisomer **19**. Conversion of **23** to the trimethyl ester **24**, $[\alpha]_D^{25}$ −28.0 (*c* 0.8, $CHCl_3$), was also carried out in the same way as for the regioisomer **20** above involving periodate cleavage and Jones oxidation (Scheme 6).

Unfortunately, epimerization of the C2 center of two trisubstituted pyrrolidines, **20** and **24**, carrying a pyridinecarboxylate on the C4 center to the natural configuration has not been successful so far despite considerable examination as both triesters were fragile under basic conditions.[4c,4g] An alternative synthesis of acromelic acids on the basis of the present results is in progress.

Acknowledgements

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