Natural Product Synthesis

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Total Synthesis of the Indole Alkaloid (±)- and (+)-Methyl *N*-Decarbomethoxychanofruticosinate**

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Methyl *N*-decarbomethoxychanofruticosinate (**1**; Figure 1)[1] belongs to a growing family of indole alkaloids with more than twenty members, namely methyl chanofruticosinates[2–5] (some of these members were also called kopreasins,[4b] prunifolines,[2d] and flavisiamines[4a,c] by different isolation groups). These alkaloids have been isolated from a variety of *Kopsia* (Apocynaceae) species, which are widely distributed in tropical Asia and have been historically used for the treatment of diseases and symptoms like pharyngitis, tonsillitis, rheumatoid arthritis,[6] and ulcerated noses in tertiary syphilis.[3] Preliminary biological studies of these natural products indicated that their existence is partially responsible for the medicinal properties of the *Kopsia* (Apocynaceae) species. For example, **1** has showed significant antitussive activity in a citric acid induced guinea pig cough model, which might be associated with the activation of δ-opioid receptors.[5] The same alkaloid also displayed relaxation activity against phenylephrine-induced contractions of rat aortas, and is the most potent agent among eleven methyl chanofruticosinate alkaloids tested.[4b] Detailed investigations of the mode of action and therapeutic potential of these alkaloids have been very limited, however, and further studies must be fueled by chemical synthesis. Structurally, methyl chanofruticosinate alkaloids all contain a caged and strained hexacyclic ring system, but are differentiated by their substituents at the 1-, 3-, 11-, 12-, 14-, and 15-positions. Other notable alkaloids isolated from the *Kopsia* species include kopsinine,[7] kopsanone,[8] and kopsihainanine A.[9] During the past decades, these natural products have received considerable attention from the synthetic community.[10] However, none of methyl chanofruticosinate alkaloids has been synthesized yet. Herein, we report the first enantioselective total synthesis of methyl *N*-decarbomethoxychanofruticosinate.

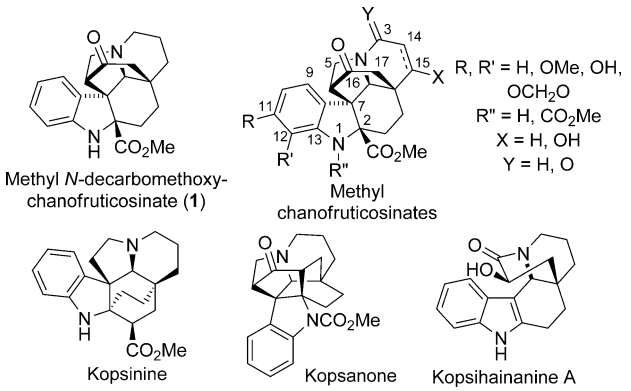

Figure 1. Structures of methyl chanofruticosinate alkaloids and related *Kopsia* alkaloids.

As outlined in Figure 2, we believed that the alkaloid **1** could be obtained by a diastereoselective attack on imine **2** with sodium cyanide and subsequent esterification. Building upon our recent successes in the syntheses of indoline alkaloids through intramolecular oxidative coupling between activated enolates and indoles,[11,12] we believed that **2** could be assembled from the pentacyclic intermediate **3** through a similar transformation. A SmI_2-mediated cyclization[13] could be used to construct the ketone **3** from the α-bromoacetamide **4**, which could be elaborated in either racemic or enantioenriched form from the commercially available 1,2,3,4-tetrahydro-4-oxocarbazole **5**.

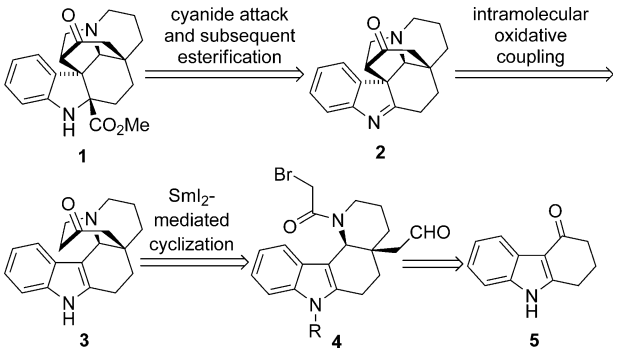

Figure 2. Retrosynthetic analysis of methyl *N*-decarbomethoxychanofruticosinate **1**.

As depicted in Scheme 1, we started our synthesis by protecting **5** using BnBr/NaH. Alkylation of the resultant benzylation product **6** with ICH_2CH_2OTBS and subsequent Michael addition with acrylonitrile provided the nitrile **7** in 45% overall yield. Reductive cyclization of **7** according to Ergun's procedure (nickel boride generated from $NiCl_2$ and

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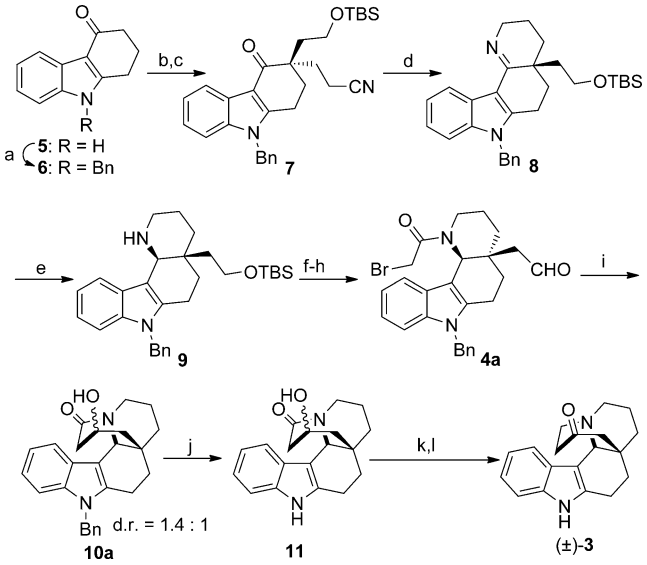
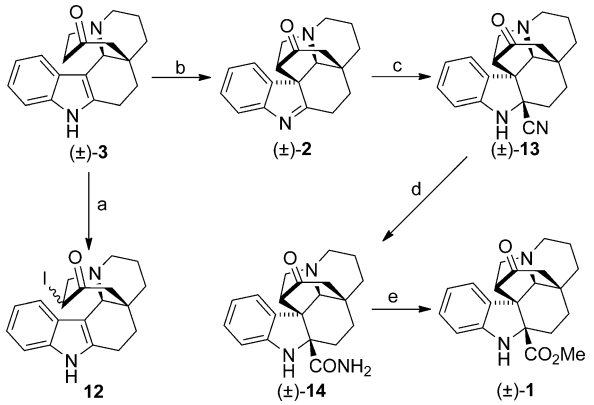


Scheme 1. Reagents and conditions: a) BnBr, NaH, DMF, 83%; b) LDA, ICH_2CH_2OTBS, THF, 65%; c) *t*BuOK, acrylonitrile, *t*BuOH, THF, 70%; d) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, $NH_2NH_2{\cdot}H_2O$, NaOH, EtOH; e) Pd/C, H_2, EtOH, 90% yield for 2 steps; f) 2-bromoacetyl chloride, CH_2Cl_2, NaOH; g) HBr, THF; h) 0.05 mol% TPAP, NMO, CH_2Cl_2, 69% yield for 3 steps; i) SmI_2, THF, 78%; j) Na, liquid ammonia, THF, *t*BuOH; k) $BH_3{\cdot}$THF; l) $Py{\cdot}SO_3$, DMSO, Et_3N, CH_2Cl_2, 52% yield from **10a**. DMSO = dimetylsulfoxide, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, NMO = *N*-methylmorpholine-*N*-oxide, TBS = *tert*-butyldimetylsilyl, THF = tetrahydrofuran, TPAP = tetrapropylammonium perruthenate.



Scheme 2. Reagents and conditions: a) LiHMDS, THF, −78 °C, 30 min, then I_2, −78 °C to RT, 35–78% yields; b) LiHMDS, THF, −78 to −40 °C, 30 min, then I_2, −40 °C to RT, 77%; c) TMSCN, MeOH, THF, 50 °C, 96%; d) K_2CO_3, H_2O_2, MeOH; e) HCl, MeOH, 45% yield for 2 steps. HMDS = hexamethyldisilazide, TMS = trimethylsilyl.

$NaBH_4$ as the catalyst, hydrazine hydrate as the hydrogen source)[14] delivered the imine **8**, which was further reduced by hydrogenation to afford the amine **9** stereoselectively. Next, acylation of **9** with 2-bromoacetyl chloride produced the corresponding amide, which was subjected to silyl ether cleavage and Ley oxidation to produce the aldehyde **4a**. The stage was then set for an intramolecular Reformatsky-like reaction to construct the seven-membered lactam. As we expected, SmI_2-mediated cyclization of **4a** proceeded smoothly at room temperature,[13] thus resulting in the β-hydroxy lactam **10a** in 78% yield as a mixture of two diastereomers. After debenzylation of **10a** with sodium and liquid ammonia in THF/*t*BuOH to yield the lactam **11**,[15] selective reduction of the amide moiety was carried out with borane to give the corresponding amino alcohol, which was oxidized into (±)-**3** under Parikh–Doering conditions in 52% overall yield. The ketone (±)-**3** was then ready for intramolecular oxidative coupling to install the caged, strained ring system in the target molecule.

Our previous studies on intramolecular oxidative coupling focused on using activated enolates.[11] Higuchi and coworkers have recently demonstrated that oxidative coupling between unactivated enolates and indoles is possible.[16] Interestingly, under our previous reaction conditions (2.2 equiv LiHMDS, −78 °C, then adding iodine),[11a,b] reaction of (±)-**3** produced the iodide **12** in 35% yield with about 50% conversion (Scheme 2). Increasing the amount of LiHMDS to 4 equivalents gave complete conversion, but **12** was the single product (78% yield). This result indicated that iodation is much faster than oxidation of the corresponding anion to the radical at lower temperatures (ca. −78 °C). To solve this problem, we decided to increase the reaction temperatures before adding iodine. After some experimentation, we were pleased to find that if iodine was added at −40 °C, the desired oxidative coupling product (±)-**2**[17] could be obtained in 77% yield. No iodation product **12** was observed in this case, thus indicating that reaction tempereature plays an essential role in differentiating reaction pathways. Next, reaction of (±)-**2** with hydrogen cyanide (generated in situ from TMSCN and MeOH) provided the amino nitrile (±)-**13**,[17] which was further treated with K_2CO_3 and hydrogen peroxide in methanol to afford the amide (±)-**14**. Finally, treatment of (±)-**14** with methanolic hydrochloride delivered the target molecule (±)-**1**, whose analytical data were in agreement with those reported for natural methyl *N*-decarbomethoxychanofruticosinate.[1] Its structure was further confirmed by X-ray analysis.[17] Noteworthy is that esterification of (±)-**13** with methanolic hydrochloride and hydrolysis of (±)-**13** using either $Ba(OH)_2$ or NaOH returned (±)-**2** as the single product, thus indicating that (±)-**13** readily undergoes cyanide elimination under both acidic and basic conditions.

In the addition of hydrogen cyanide to (±)-**2**, only one diastereomer was observed. This phenomenon could be rationalized by the X-ray structure analysis of (±)-**2** (Figure 3). A strong 1,3-diaxial interaction occurs if the cyanide attacks the imine moiety from the *Re* face. Thus,

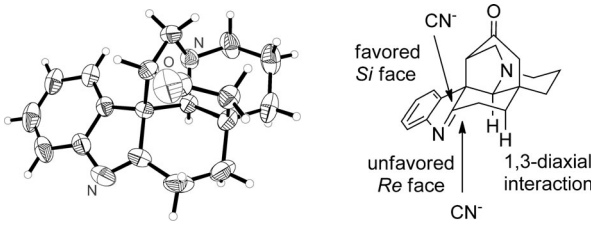
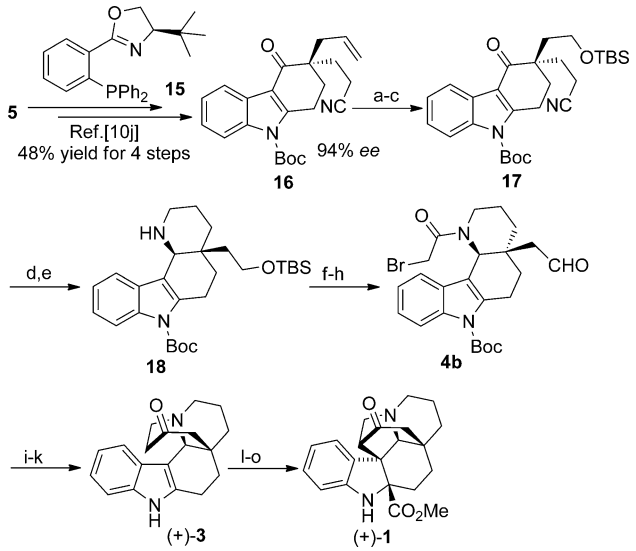


Figure 3. Stereochemical course in addition of hydrogen cyanide to the imine (±)-**2**.

nucleophilic attack from the *Si* face is favored and (±)-**13** was isolated as a single product.

Very recently, the groups of Lupton[10i] and Shao[10j] independently revealed that enantioselective palladium-catalyzed decarboxylative allylation[18] of carbazolones could produce enantioenriched carbazolones bearing a quaternary carbon center. We envisioned that their products could be perfectly applied to the asymmetric synthesis of **4**. We therefore attempted to develop an enantioselective synthesis of *N*-decarbomethoxychanofruticosinate using this methodology. As outlined in Scheme 3, using the phosphine **15** as a ligand, the carbazolone **16** was prepared from **5** in four steps



Scheme 3. Reagents and conditions: a) K_2OsO_4, $NaIO_4$; b) $NaBH_4$, EtOH, CH_2Cl_2; c) TBSCl, imidazole, CH_2Cl_2; 91% yield for 3 steps; d) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, $NH_2NH_2{\cdot}H_2O$, NaOH, EtOH; e) Pd/C, H_2, EtOAc, 88% yield for 2 steps; f) 2-bromoacetyl chloride, CH_2Cl_2, NaOH; g) HBr, THF; h) 0.05 mol% TPAP, NMO, CH_2Cl_2, 68% yield for 3 steps; i) SmI_2, THF, 78%; j) $BH_3{\cdot}$THF, then HCl; k) $Py{\cdot}SO_3$, DMSO, Et_3N, CH_2Cl_2, 74% yield for 2 steps; l) LiHMDS, THF, −78–40 °C, 30 min, then I_2, −40 °C to RT, 77%; m) TMSCN, MeOH, THF, 96%; n) K_2CO_3, H_2O_2, MeOH; o) HCl, MeOH, 45% yield for 2 steps.

in 48% overall yield and 94% *ee*. Oxidative cleavage of the allyl group in **16**, subsequent reduction with $NaBH_4$, and protection with TBSCl provided the silyl ether **17** in 91% yield. Reductive cyclization of **17** and subsequent hydrogenation of the resultant imine gave rise to **18**, which was subjected to acylation, deprotection, and oxidation to yield the aldehyde **4b**. After intramolecular Reformatsky-like reaction of **4b**, reduction of the amide moiety and oxidation of the alcohol to give the ketone (+)-**3**, and (+)-**1** was assembled by following a same procedure as shown in Scheme 2.

In conclusion, we have accomplished the first total synthesis of methyl *N*-decarbomethoxychanofruticosinate, which features a SmI_2-mediated intramolecular Reformatsky-like reaction to create its seven-membered ring and an intramolecular oxidative coupling to install its caged and strained ring system. The synthesis requires only 16 linear steps (racemic) or 19 linear steps (enantioselective) from commercially available **5**. This route should allow the assembly of the other members in methyl chanofruticosinate family by tuning the substituents in carbazolones **5**–**7**, and therefore prompts the synthetic studies of these alkaloids and their analogues, as well as their structure–activity relationship investigations. Additionally, our observations during the oxidative coupling of the indole moiety with activated and unactivated enolates should serve as precedents for mechanistic studies and further synthetic applications of this strategy.

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[17] CCDC 958949 (**1**), 958947 (**2**), and 958948 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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