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Protected Cyanohydrins in the Synthesis of Rotenoids: (±)-Munduserone and (±)-*cis*-12a-Hydroxymunduserone

Evin H. Granados-Covarrubias and Luis A. Maldonado*

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, México, 04510, D.F., México

lammg@servidor.unam.mx

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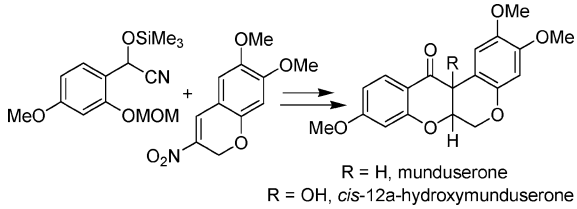

Short synthetic routes to the natural products (±)-munduserone **1** and (±)-*cis*-12a-hydroxymunduserone **9** from protected cyanohydrin **5** and nitrochromene **4** are described. The key coupling reaction of **4** and **5** gave under inverse addition conditions **9** (28%) and **2b** (21%), while under normal addition conditions, a mixture of **9** (20%), dehydromunduserone **10** (9%), and enone **2b** (10%) was obtained. (±)-Munduserone **1** is easily obtained from both **2b** and **9** by 10% methanolic HCl (86%) and Zn/AcOH (71%) treatments, respectively.

The rotenoids are a biogenetically derived class of flavonoids featuring the chromano[3,4-*b*]chromanone framework.[1] Interest in this class of compounds is high because many members exhibit impressive antitumor activity in human tumor cell lines.[2] In this context, it is also worth mentioning that the rotenoid deguelin is considered a highly promising cancer chemopreventive agent.[3]

In 1960, Finch and Ollis reported the isolation and structural elucidation of the simplest natural rotenoid munduserone **1**, obtained from the bark of *Mundulea sericea*.[4c] This was followed by a report from the same group on the total synthesis of **1**, though in an unstated overall yield.[5i] Later on, other interesting but quite inefficient routes have also been reported.[5] Despite limited biological activity, **1** captured our attention as a convenient target for demonstrating novel synthetic strategies, for development of general approaches to more complex rotenoids. Herein, we report concise syntheses of **1** and its natural *cis*-12a-hydroxy derivative **9**, which to our knowledge is the first total synthesis of this compound.[6]

On the basis of the premise that rotenoids are indeed isoflavanones with an additional six-membered oxygen heterocycle, the strategy for **1** was an elaboration of our recent methodology to synthesize isoflavanones.[7] The key step was thus envisioned to be the coupling of protected cyanohydrin **5** (easily available, in principle, from commercial **7**) and the known[8] nitrochromene **4** (prepared in one step from **6**) to give **3** (Scheme 1). After removal of protecting/activating groups, the known enone **2a** should be obtained, which has been cyclized into munduserone in high yield,[5e] under mildly basic catalytic conditions (AcONa/EtOH). This is important for an eventual formal synthesis of munduserone.

Nitrochromene **4** was prepared as reported[8] by using the one-step di-*n*-butylamine-catalyzed condensation of 4,5-dimethoxysalicylaldehyde **6**[9] and freshly prepared nitroethylene in $CHCl_3$ solution. Unfortunately, in our hands, yields were only 20−25% (the reported yield is 72%) but unreacted aldehyde could be recovered and recycled until total consumption was achieved. On the other hand, the "protected cyanohydrin" **5** was prepared in 78% overall yield from **7** by methoxymethylation

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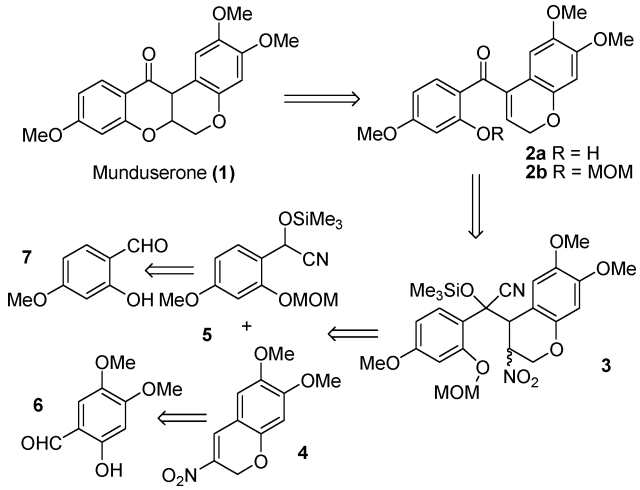
SCHEME 1. Retrosynthetic Analysis for Munduserone Based on Protected Cyanohydrin Chemistry



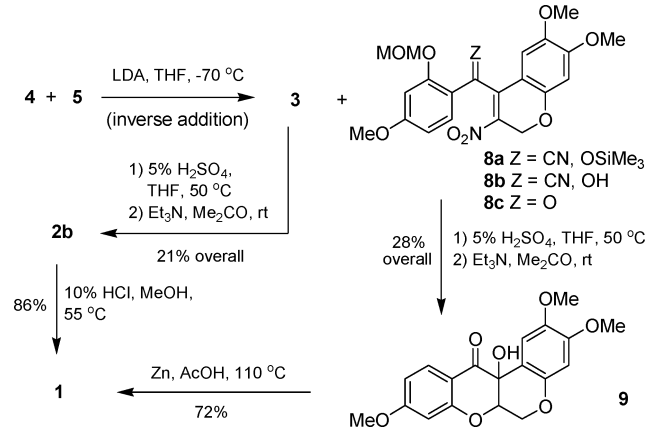
(NaH, $ClCH_2OMe$,[10] THF) and cyano-*O*-trimethylsilylation[11] (Me_3SiCN, catalytic KCN and 18-crown ether, C_6H_6).

With the precedent that lithium bases promoted hydride migration during the conjugate addition of an analogue of protected cyanohydrin **5** to (*E*)-4-methoxy-β-nitrostyrene to give a 1:1 mixture of "normal" and "dehydro" adducts, our first choice to perform this coupling was using KH as base in DME, as was previously found useful in our formononetine synthesis.[7] However, complex product mixtures were obtained, from which only the isomeric 6,7-dimethoxy-3-nitro-2-chromene could be isolated in low yield and characterized. Probably the basicity of the potassium carbanion of **5** was responsible for isomerization, but attempts to avoid the problem by working under inverse addition conditions also failed, at least in part because of the relatively low solubility of the potassium carbanion in DME, which resulted in clogging of the transfer cannula.

Hence, we decided to use LDA as the coupling reaction base with the expectation that chromatographic separation of the "normal" and "dehydro" adducts from the reaction mixture would be feasible. Coupling between **4** and **5** was performed under both normal (A) and inverse (B) addition conditions to give mixtures of adducts which, without purification, were successively submitted to our usual mild acid (5% aqueous H_2SO_4, THF, 50 °C) and base treatments (Et_3N, Me_2CO, rt) for *O*-trimethylsilyl cleavage and HCN and HNO_2 removals, respectively. After silica gel column chromatography, from conditions B two fractions were obtained and identified as the desired less polar "normal" enone adduct **2b** (21% yield) and surprisingly, the more polar natural product *cis*-12a-hydroxymunduserone **9**[6] (28% yield) (Scheme 2). Rotenoid **9** is clearly derived from the dehydro adduct **8a** whose preferential formation in this experiment can be rationalized by the stronger electron donor effect of the trioxy-substituted ring, facilitating the required hydride migration to the lithium cation, as compared with the single methoxy-substituted aromatic ring used in our formononetine synthesis.[7]

The structure of enone **2b** was derived from its spectroscopic data and its acid-catalyzed conversion into the natural product munduserone **1** (86% yield). In this cyclization, the intermediate

SCHEME 2. Total Synthesis of (±)-Munduserone (1) and (±)- *cis*-12a-Hydroxymunduserone (9)



hydroxyenone **2a** was not isolated. Furthermore, we have also converted **9** into **1** in 71% yield with Zn in hot AcOH,[12] a considerable improvement for this four-step known conversion.[13]

On the other hand, from conditions A two fractions were also obtained with identical R_f values as those obtained for the corresponding fractions of conditions B. The less polar fraction was identified as **2b** (10% yield), but the more polar fraction contained **9** in admixture with dehydromunduserone **10**. These compounds, separable only by further preparative TLC (99:1, C_6H_6/MeOH, three elutions), were obtained in yields of 20% and 9%, respectively. Dehydromunduserone **10** is also a known compound prepared as an intermediate in some previous munduserone syntheses.[5f−i] Hence, our preparation of **10** represents a new formal synthesis of munduserone.

Regarding the mechanism of this unusual reaction, and though our analysis remains speculative, we propose the formation of a common intermediate **11** that can undergo proton loss to dehydromunduserone **10** (path a) or a 1,2-hydride shift to the *p*-quinoid cation **12** followed by water addition, to give *cis*-12a-hydroxymunduserone **9** (path b). The common intermediate **11** is, in turn, obtained from nitroenone **8c**, the expected product obtained after deprotection of the initially formed dehydro adduct **8a**, as depicted in Scheme 3. Although we have not attempted to isolate the presumably formed, acid-sensitive "normal" adducts **3** (four stereoisomers are possible) and "dehydro" adduct **8a** from the complex reaction mixture for characterization, the latter is a reasonable starting point for the mechanistic proposal based on our previous results.[7,14]

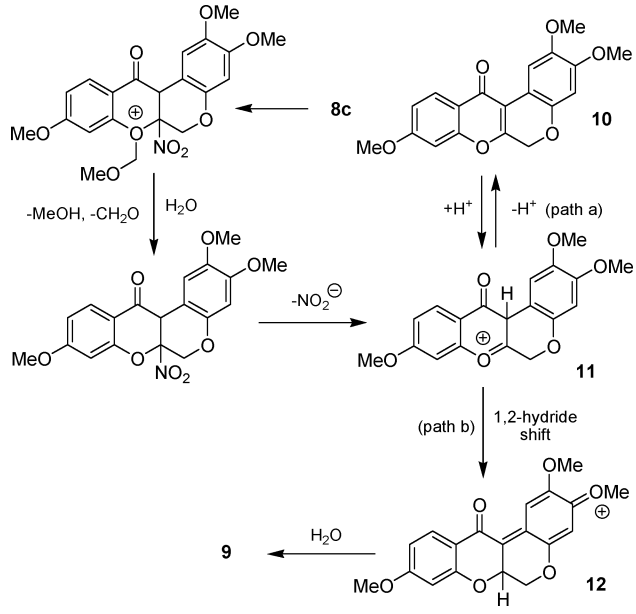
In summary, concise total synthesis of the rotenoids (±)-munduserone **1** and (±)-*cis*-12a-hydroxymunduserone **9** have been achieved by using a new approach that involves conjugate addition of the lithium carbanion of an aromatic protected cyanohydrin **5** to nitrochromene **4** as the key reaction. Although the coupling reaction yielded mixtures of two or three products, depending on whether inverse or normal addition conditions were used, all these compounds converged into **1** by simple transformations. Furthermore, as (with few exceptions) natural rotenoids have the same dimethoxy-substituted ring A, which is delivered by nitrochromene **4**, this approach can be applied, in principle, to other biologically more interesting rotenoids. This should be very simple because selection of the appropriate aromatic aldehyde is the only challenge. We are pursuing further

(12) To the best of our knowledge, this reaction has been attempted only with the unnatural trans isomer of 12a-hydroxymunduserone.[5b,c]

(13) See ref 6b for the two-step conversion of **9** → dehydromunduserone **10** and refs 5f−i for the two-step conversion of **10** → **1**.

(14) However, we are aware that the absence of **10** under inverse addition conditions is the main challenge of our view of the mechanism. See the Supporting Information for additional data on this issue.

SCHEME 3. Mechanistic Proposal for Rotenoid Formation



experiments to improve yields, to learn more about the mechanism of the unusual coupling reaction, and hopefully, to find experimental conditions suitable for fine-tuning the preferential formation of normal enone adducts or rotenoids, as desired.

Experimental Section

Coupling of Protected Cyanohydrin 5 and 6,7-Dimethoxy-3-nitro-3-chromene 4 (Inverse Addition). To a stirred solution of 1.7 mmol of LDA in 5 mL of dry THF (prepared in the usual way from 0.17 g (1.7 mmol) of dry diisopropylamine and 1.2 mL of a 1.47 M solution of *n*-BuLi in hexanes (1.7 mmol)) at −70 °C was added a THF solution (3 mL) of protected cyanohydrin **5** (0.386 g, 1.3 mmol). The resulting yellow solution was stirred at −70 °C for 15 min, and added dropwise via cannula to a cooled (−70 °C) stirred solution of **4** (0.31 g, 1.3 mmol) in 5 mL of THF. The red solution was stirred at −70 °C for 40 min, warmed at rt, quenched with 6 mL of Na_2HPO_4 buffer (pH 7.3), and extracted with AcOEt. The combined organic layer was washed with brine and dried. Concentration afforded a thick red oil that was dissolved in THF (5 mL) and 5 mL of 5% aqueous H_2SO_4 was added. The stirred mixture was heated in an oil bath at 55 °C for 14 h, cooled at rt, quenched with saturated $NaHCO_3$ aqueous solution, and extracted with AcOEt. The combined organic layer was washed with brine and dried. Concentration afforded a red gum that was dissolved in 10 mL of Me_2CO, 0.7 mL of Et_3N was added, and the dark solution was stirred at rt for 14 h. The volatiles were removed at reduced pressure, the residue was partitioned between AcOEt and brine, and the organic layer was dried. Concentration afforded a red viscous oil that was chromatographed on flash silica gel (4:1, hexanes/AcOEt) to give two main fractions. The fast moving fraction was enone **2b** (0.131 g, 21%) and the slow moving fraction was (±)-**9** (0.163 g, 28%).

Enone 2b: pale yellow oil; IR (film) ν 1655, 1603, 1508, 1462, 1262, 1157, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 1H), 7.13 (s, 1H), 6.7 (d, J = 2.4 Hz, 1H), 6.6 (dd, J = 8.5, 2.4 Hz, 1H), 6.48 (s, 1H), 6.08 (t, J = 4.2 Hz, 1H), 5.02 (s, 2H), 4.76 (d, J = 4.2 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H), 3.36 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 163.8, 158.0, 149.9, 148.7, 143.4, 136.8, 132.2, 126.2, 122.3, 112.4, 108.8, 106.8, 101.6, 100.9, 100.4, 94.9, 64.8, 56.2, 55.9, 55.5 ppm; MS (EI) (*m*/*z*, %) 386 (M^+, 50), 341 (56), 190 (25), 178 (46), 151 (38), 57 (100); HRMS (FAB) calcd for $C_{21}H_{22}O_7$ (M^+) 386.1366, found 386.1364.

(±)-*cis*-12a-Hydroxymunduserone 9: white solid; mp 284−286 °C; IR (KBr) ν 3448, 1676, 1610, 1509, 1259, 1200, 1162, 1104, 1035 cm^{-1}; ^1H NMR (300 MHz, C_3D_6O) δ 7.79 (d, J = 9 Hz, 1H), 6.62 (dd, J = 9, 2.7 Hz, 1H), 6.62 (s, 1H), 6.48 (s, 1H), 6.41 (d, J = 2.7 Hz, 1H), 5.49 (s, OH, exchanges with D_2O), 4.69 (dd, J = 2.1, 1.2 Hz, 1H), 4.58 (dd, J = 12, 2.1 Hz, 1H), 4.47 (dd, J = 12, 1.2 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.59 (s, 3H) ppm; ^{13}C NMR (75 MHz, C_3D_6O) δ 191.7, 167.5, 163.1, 152.5, 149.7, 144.6, 129.6, 112.7, 112.3, 111.4, 109.8, 101.9, 101.2, 77.0, 68.5, 64.6, 56.8, 56.2, 55.9 ppm; MS (EI) (*m*/*z*, %) 358 (M^+, 38), 208 (100), 151 (12); HRMS (FAB) calcd for $C_{19}H_{18}O_7$ (M^+) 358.1053, found 358.1053.

(±)-Munduserone 1: (a) From Enone 2b. To a stirred solution of **2b** (0.03 g, 0.078 mmol) in dry MeOH (1.5 mL) was added a 10% solution of HCl in MeOH (1.5 mL). The reaction mixture was stirred and heated in an oil bath at 65 °C for 2 h, cooled at rt, and quenched with saturated aqueous $NaHCO_3$ solution. The volatiles were removed at reduced pressure then extracted with CH_2Cl_2, and the combined organic fractions were washed with brine and dried. Concentration afforded a crystalline brown solid that was chromatographed on flash silica gel (17:3, hexanes/AcOEt) to give 0.023 g (86%) of crystalline (±)-**1**. Mp 169−170 °C (lit.[4c] mp 171−172 °C); IR (KBr) ν 2939, 1675, 1615, 1516, 1452, 1277, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87 (d, J = 8.7 Hz, 1 H), 6.76 (s, 1 H), 6.57 (dd, J = 8.8, 2.4 Hz, 1 H), 6.46 (s, 1 H), 6.42 (d, J = 2.4 Hz, 1 H), 4.9 (dt, J = 12.0, 4.2, 3.0 Hz, 1 H), 4.62 (dd, J = 12.0, 3.0 Hz, 1 H), 4.18 (d, J =12.0 Hz, 1 H), 3.84 (d, J = 4.2 Hz, 1 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 3.75 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$) δ 189.2, 166.5, 162.7, 149.5, 147.4, 143.9, 129.3, 112.7, 110.6, 110.4, 104.7, 101.0, 100.6, 72.4, 66.2, 56.3, 55.8, 55.6, 44.5; MS (EI) (*m*/*z*, %) 342 (M^+, 53), 192 (100), 83 (45); HRMS (EI) calcd for $C_{19}H_{18}O_6$ (M^+) 342.1103, found 342.1107.

(b) From (±)-*cis*-12a-Hydroxymunduserone 9. A stirred mixture of **9** (0.15 g, 0.43 mmol), AcOH (15 mL), and Zn dust (3 g, 45 atom·mg) was heated in an oil bath at 115 °C for 45 min. The suspension was cooled at rt, filtered, and thoroughly washed with hot CH_2Cl_2. The solution was evaporated to dryness with the aid of first a rotavapor and then an oil pump, then the residue was dissolved again in CH_2Cl_2 (25 mL) and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The dried solution was concentrated and the solid residue was cromatographed on flash silica gel (17:3, hexanes/AcOEt) to give 0.102 g of (±)-**1** (71%).

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Supporting Information Available: Preparation and characterization of **5**, experimental conditions for coupling of **4** and **5** by the normal addition protocol, spectroscopic data for **10**, additional data for the proposed reaction mechanism, and ^1H and ^{13}C NMR spectra for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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