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Intramolecular 1, 6-Conjugate Addition Approach for Construction of the Hydrindane Framework: Total Synthesis of (±)-Coronafacic Acid

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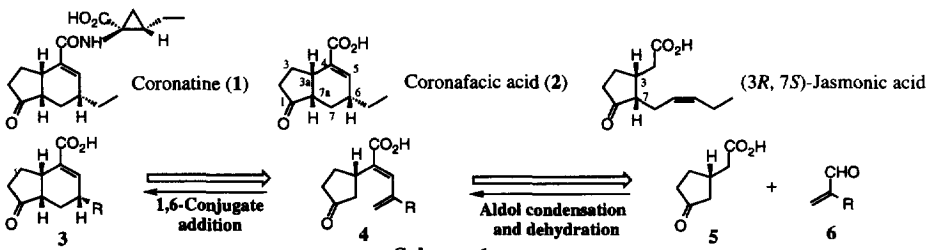
Abstract: A new approach for the construction of the hydrindane framework has been achieved by intramolecular 1, 6-conjugate addition under some basic conditions. The precursors, α, β, γ, δ-unsaturated esters (**11a-11d**) were synthesized from the ester **8** and acrolein derivatives (**6a-6d**) *via* aldol condensation. This methodology was applied to the total synthesis of (±)-coronafacic acid and its analogues. Copyright © 1996 Elsevier Science Ltd

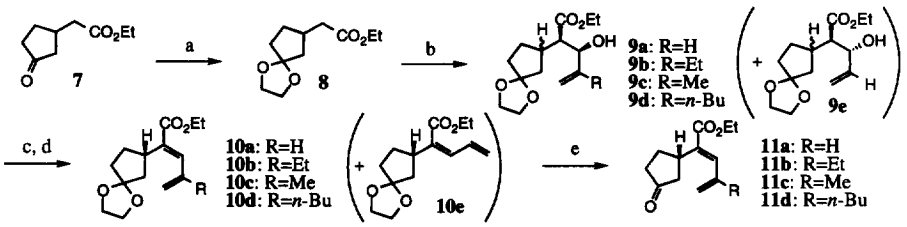
There are many biologically active natural products possessing the hydrindane framework as such or one part of a polycyclic structure. Since they are attractive synthetic targets, various methods for the construction of the hydrindane framework have been developed and applied to natural product synthesis.[1] Among them, a plant toxin, coronatine **1** and its carboxylic acid component, coronafacic acid **2**, isolated from *Pseudomonas syringae* pv. *atropurpurea* as a chlorosis-inducing factor on the leaves of Italian ryegrass, have a 1-hydrindanone framework.[2] Recently, there has been much interest in coronatine which has been shown to exhibit the various biological activities of jasmonic acid, known as an endogenous plant-growth regulator and signal transmitter. Furthermore, the biological activities of coronatine are 100 to 10,000 times higher than those of jasmonic acid. Coronafacic acid itself exhibits equal or slight weak jasmonic acid-like activity.[3] Previous syntheses of **2** fall under several categories which are classified as annulation of cyclohexene,[4] inter- and intramolecular Diels-Alder reaction,[5] anionic oxy-Cope rearrangement of bicyclic compounds,[6] and fragmentation of tricyclic compounds.[7] In this paper, a new approach for construction of the hydrindane framework *via* intramolecular 1, 6-conjugate addition, leading to the total synthesis of coronafacic acid, is described. Although a few examples of annulation using intermolecular 1, 6-conjugate addition have been reported,[8] intramolecular 1, 6-conjugate addition has not been applied to annulation-type reaction.



Scheme 1

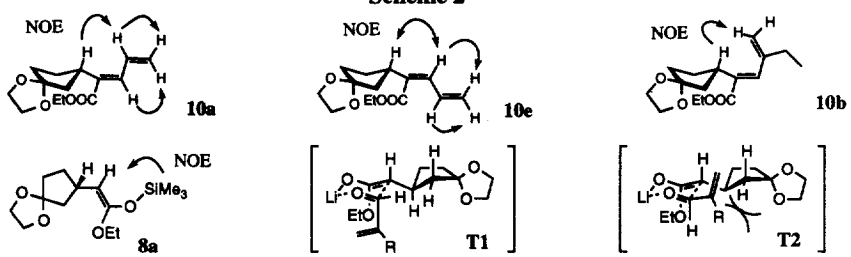
Our strategy is shown in Scheme 1. A compound **3** (R=H, or alkyl) is retrosynthesized to α, β, γ, δ-unsaturated carboxylic acid **4** and further to cyclopentanone carboxylic acid **5** and acrolein derivative **6**. Aldol condensation between **5** and **6**, and subsequent dehydration would provide **4**. Intramolecular 1, 6-conjugate addition of **4** would provide **3** and the desired stereogenic centers (C_6 and C_{7a}) would be controlled in this stage. Furthermore, this route would supply analogues of **2** by the replacement of the alkyl group in **6**.

A known ester **7** was synthesized from 2-cyclopentenone and magnesium monomethyl malonate *via* malonic ester synthesis.[9] The carbonyl group of **7** was protected as a cyclic acetal to give **8**[10] in 89% yield. Aldol condensation was first achieved between lithium enolate of **8** and acrolein (**6a**: R=H) to give a mixture of hydroxy ester (**9a**:**9e** = *ca.* 4:1) in 93% yield. Since the relative stereochemistry between the ethoxycarbonyl group and the hydroxyl group could not be determined at this stage, the mixture was further converted to α, β, γ, δ-unsaturated ester by the conventional method. Mesylation of the hydroxyl group and subsequent elimination with DBU provided (*E*)-isomer **10a** and (*Z*)-isomer **10e** in a ratio of *ca.* 4:1. The geometry of the newly formed olefin was reasonably explained by ^{1}H-^{1}H-NOE experiment. Therefore, the *syn*- and *anti*-relationship between the ethoxycarbonyl group and the hydroxyl group in **9a** and **9e** was proved, respectively. When 2-ethylacrolein (**6b**: R=Et) was next used for aldol condensation, diastereomeric hydroxy ester **9b** possessing *syn*-relationship was selectively obtained in 92% yield. By the same method as described above, **9b** was converted to a diene, (*E*)-isomer **10b**, as the sole product in 83% yield (2 steps). ^{1}H-^{1}H-NOE experiment gave only one NOE-enhancement, which revealed that **10b** possesses (*E*)-geometry and *s-cis* conformation considered favorable for the next cyclization. 2-Methylacrolein (**6c**: R=Me) and 2-*n*-butylacrolein (**6d**: R=*n*-Bu) were also converted to **10c** and **10d**, respectively, by the same three-step method. Transacetalization of **10a-10d** provided ketones **11a-11d**, respectively, in almost quantitative yield. Thus, the requisite precursors for intramolecular 1, 6-conjugate addition were set up.



(a) *p*-TsOH, ethylene glycol / benzene, 89% (b) LDA / THF then aldehyde **6a** (R=H), 93%; **6b** (R=Et), 92%; **6c** (R=Me), 82%; **6d** (R=*n*-Bu), 90% (c) MsCl, DMAP / CH_2Cl_2 (d) DBU / CH_2Cl_2 , **10a**:**10e** = 4:1 (82%, 2 steps);**10b** (83%, 2 steps); **10c** (61%, 2 steps); **10d** (85%, 2 steps) (e) *p*-TsOH / acetone, 99%

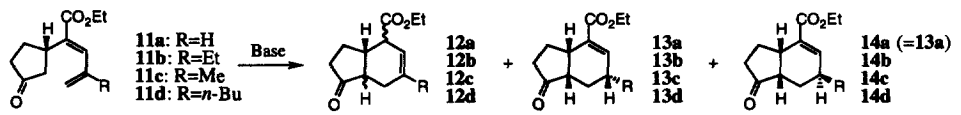
Scheme 2



These results show that aldol condensation proceeds stereospecifically in the case of using the 2-alkyl-substituted acrolein. In order to clarify the mechanism of aldol condensation, the geometry of lithium enolate was determined as the corresponding silyl enol ether **8a**. The NOE-enhancement of the olefinic proton was observed by the irradiation of the methyl protons in the TMS group. This result means that the (*E*)-enolate forms stereoselectively and contributes to the transition state of the aldol condensation. In two possible 6-membered chair-like transition states (**T1** and **T2**), **T1** predominates over **T2** because the steric hindrance between the bulky cyclopentane moiety of the enolate and the alkenyl moiety of the aldehyde contributes unfavorably in **T2**. In **T1**, the interaction between the cyclopentane moiety and the hydrogen is not significant in contrast to **T2**. When acrolein (**6a**, R=H) lacking an alkyl group on the olefin is used, aldol condensation proceeds to some extent *via* **T2** because of the relaxation of steric hindrance. Therefore, a mixture of **9a** and **9e** was obtained in the ratio of *ca.* 4:1. When 2-alkylacroleins (**6b-6d**) possessing an alkyl group are used, aldol

condensation proceeds exclusively *via* **T1** to give *syn*-products (**9b-9d**).

Intramolecular 1, 6-conjugate addition was carried out under some basic conditions (Scheme 3, Table. 1). α, β-Unsaturated esters (**13** and **14**) and / or γ, δ-unsaturated ester (**12** as a mixture of three diastereomers) were obtained under the conditions as stated in Table 1. When pyrrolidine was used as a base, an enamine generated *in situ* might play the role of donor. Of course, an enolate anion becomes the donor in the case of using EtONa or *t*-BuOK. Treatment of **11a** with pyrrolidine (1.0 eq.) in PhH-*t*-BuOH gave **12a** and **13a** (=**14a**) in 7:1 ratio (70% yield, entry 1). By using EtONa (0.5 eq.) in EtOH, **13a** was only obtained in 20% yield (entry 2). The yield was decreased by the intermolecular addition of an ethoxyl group to **11a**. When a catalytic amount of pyrrolidine (0.1 eq.) was used, **11b** was converted to **12b** in 94% yield (entry 3). When a catalytic amount of EtONa (0.1 eq.) was used, the cyclization of **11b** also proceeded to give **12b**, **13b**, and **14b** in 8:5:1 ratio (80% yield, entry 4). In contrast to the catalytic reaction, when 3.0 eq. of NaOEt was used, only α, β-unsaturated esters (**13b** and **14b**: separable by using a Lobar® column) were obtained in 3:1 ratio and in 71% yield (entry 5). This result demonstrates that the desired compound **13b**, possessing the three stereogenic centers, could be synthesized in one step (53% yield) *via* intramolecular 1, 6-cojugate addition. In particular, our new approach is effective for the construction of 1-hydrindanone framework such as **13b**. Under the same conditions, prolongation of the reaction time (48 h) resulted in decreasing the diastereoselectivity (**13b**:**14b**=1.8:1).[11] By using a stronger base (*t*-BuOK), the yield was decreased by a side reaction (entry 6). Under the same conditions as stated in entry 3, **11c** and **11d** were converted to **12c** and **12d** in high yield, respectively (entries 7 and 8). In the cases of using pyrrolidine, γ, δ-unsaturated ester **12** was obtained predominantly (entry 1) or exclusively (entries 3, 7, 8). It would be considered that 1, 6-addition would proceed first in *cis*-relationship between H_{3a} and H_{7a} and then epimerization at the C_{7a} stereogenic center occurs next to give **12** possessing *trans*-relationship. Migration of the double bond from γ, δ– to α, β-position, namely, isomerization from **12** to **13** and **14**, could be achieved by the treatment of **12** with EtONa in EtOH at r.t. or DBU in PhH under reflux in 70-90% yield.[11]



Scheme 3

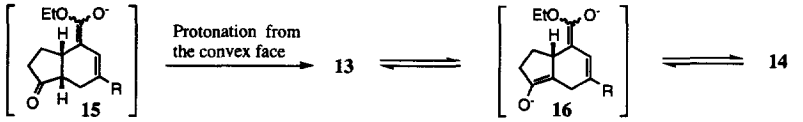
Table. 1 Construction of 1-Hydrindanones *via* Intramolecular 1,6-Conjugate Addition

Entry	Substrate	Conditions Base (eq.) / Solvent / temp. / time	Yield (%)	Product Ratio[a] 12 : 13 : 14
1	**11a**	pyrrolidine (1.0) / PhH-*t*-BuOH / r. t. / 48 h	70	7 : 1
2	**11a**	EtONa (0.5) / EtOH / r. t. / 9 h	20	0 : 1
3	**11b**	pyrrolidine (0.1) / PhH-*t*-BuOH / r. t. / 24 h	94	1 : 0 : 0
4	**11b**	EtONa (0.1) / EtOH / r.t. / 24 h	80	8 : 5 : 1
5	**11b**	EtONa (3.0) / EtOH / r.t. / 24 h	71	0 : 3 : 1
6	**11b**	*t*-BuOK (1.0) / *t*-BuOH / r.t. / 24 h	20	23 : 4 : 1
7	**11c**	pyrrolidine (0.1) / PhH-*t*-BuOH / r. t. / 24 h	91	1 : 0 : 0
8	**11d**	pyrrolidine (0.1) / PhH-*t*-BuOH / r. t. / 24 h	89	1 : 0 : 0

a) The ratio was determined by ^{1}H-NMR.

In connection with the reaction mechanism, it would be considered that the diastereoselectivity of **13** and **14** would be influenced by kinetic and thermodynamic factors. Under the conditions using NaOEt (entry 5 and isomerization from **12**), dienolate **15** would be formed as an intermediate. The kinetic protonation in **15**, would occur predominantly from the convex face to give **13** as the major product. In a possible bis-enolate **16** derived from **13**, increasing the planar character, the diastereofacial selectivity of protonation would decrease to give **13**

and **14** in a certain ratio. Therefore, **13** would isomerize to **14** *via* **16** until the reaction attains equilibrium. Actually, the diastereoselectivity was decreased with the time-course as described previously. Study to elucidate the reaction mechanism and to increase the diastereoselectivity is under way.



Acidic hydrolysis (3N HCl, reflux) of **13b** provided (±)-coronafacic acid **2** in 70% yield, whose spectral data were identical with those of the natural product in all respects (except for the specific rotation). The overall yield was 25% starting from the known compound **7** in 7 steps. In this way, an efficient total synthesis of **2** has been accomplished by using the intramolecular 1, 6-conjugate addition as the key step. 6-*Epi*-coronafacic acid and the 6-substituted derivatives (R=H, Me, and *n*-Bu in **3**) of **2** were also obtained from the corresponding esters (**14b**, **13a**, **13c**, and **13d**,[12] respectively) by acidic hydrolysis. These analogues would provide useful information on the structure-activity relationship of coronatine, coronafacic acid, and jasmonic acid. Furthermore, in principle, our route provides the optically active **2** by using the optically active **7** as the starting material. The asymmetric total synthesis of **2** directed toward **1** is now in progress.

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10. Satisfactory spectroscopic data were obtained for all new compounds.
11. The ratio of **13** and **14** varied up to *ca.* 1:1 with the time-course.
12. The esters **13c** and **13d** were obtained by the isomerization of **12c** and **12d**, respectively.

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