Natural Product Synthesis

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Unified Total Synthesis of 3-*epi*-Ryanodol, Cinnzeylanol, Cinncassiols A and B, and Structural Revision of Natural Ryanodol and Cinnacasol

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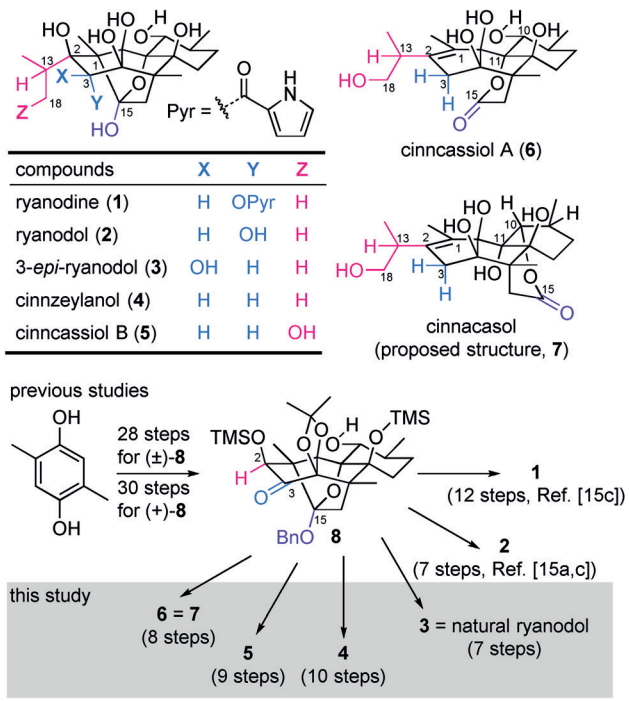
Abstract: *Ryanodane diterpenoids structurally share an extremely complex fused ring system, but differ in the substitution patterns of the hydroxy groups. Since these congeners exhibit various biologically important functions, their efficient chemical constructions have been greatly anticipated. We previously accomplished the total synthesis of ryanodine (**1**) using pentacycle **8** as the advanced intermediate. Here, we report the unified total syntheses of four distinct diterpenoids, 3-epi-ryanodol (**3**), cinnzeylanol (**4**), cinncassiols B (**5**), and A (**6**), from **8**, all within 10 steps. A series of highly optimized chemo- and stereoselective reactions and protecting-group manipulations enabled assembly of the densely oxygenated structures of **3**–**6**. Furthermore, the present synthetic studies established the C13S stereochemistry of **5**–**7** and revised the proposed structures of natural ryanodol (**2**) and cinnacasol (**7**) to be those of **3** and **6**, respectively.*

Terpenoids constitute one of the largest groups of natural products.[1] The enormous structural diversity presented by this class of secondary metabolites ensures a broad range of biological properties, and terpenoids play a significant role in the discovery and development of pharmaceuticals.[2,3] Ryanodane diterpenoids, designated after ryanodine (**1**; Scheme 1), possess one of the most prominent and complex molecular frameworks among the numerous known terpenoids. The twenty carbon atoms of these molecules are uniquely organized into a fused polycycle, and are densely substituted by multiple oxygen atoms. Since the structure elucidation of **1** in 1968,[4] a number of analogous structures have been disclosed and share the same molecular framework with distinct positions and orientations of oxygen-based functionalities.

While it was shown in 1951 that basic hydrolysis of **1** generated synthetic ryanodol (**2**) by ejection of pyrrole-2-carboxylic acid,[5] the same compound was reported to be found from the tree *Persea indica* in 1990.[6] Cinnzeylanol (**4**)[7] and cinncassiol B (**5**)[8] are both derived from *Cinnamomi cortex*, and their structures correspond to 3-deoxy-ryanodol and 3-deoxy-18-hydroxy-ryanodol, respectively. On the other hand, cinncassiol A (**6**)[9] and cinnacasol (**7**)[10] were revealed to be the dehydrated structure of **5**, but they differ in the cyclization mode of the C15 lactone. Collectively, these structures have attracted intense attention from chemists and biologists alike on account of their diverse biological activities such as channel-modulatory (**1**),[11] insecticidal (**2**, **4**),[6] *anti*-complement (**4**–**6**),[7–9] and immunosuppressive activities (**7**).[12] Although interaction of **1** with intracellular calcium release channels is well investigated, little is known regarding the modes of action of the other ryanodane diterpenoids. Structure–activity relationship (SAR) studies of these compounds can pinpoint essential functionalities within a molecule for each activity and enable optimization of its specific function. However, the SAR data remain restricted by the lack of efficient and divergent synthetic strategies for construction of these complex architectures.[13,14]



compounds	X	Y	Z
ryanodine (**1**)	H	OPyr	H
ryanodol (**2**)	H	OH	H
3-*epi*-ryanodol (**3**)	OH	H	H
cinnzeylanol (**4**)	H	H	H
cinncassiol B (**5**)	H	H	OH

Scheme 1. Structures and unified total syntheses of ryanodane diterpenoids.

Most recently, we disclosed the total synthesis of ryanodine (**1**) and ryanodol (**2**).[15] The pentacyclic ring system **8** was constructed from 2,5-dimethylbenzene-1,4-diol in both racemic and enantiopure forms, and was transformed into **1** and **2** through C2- and C3-functionalizations (Scheme 1). We envisioned that this novel strategy would offer a unique opportunity to modify the C2- and C3-substitution patterns of the ryanodane diterpenoids. Herein, we report the late-stage

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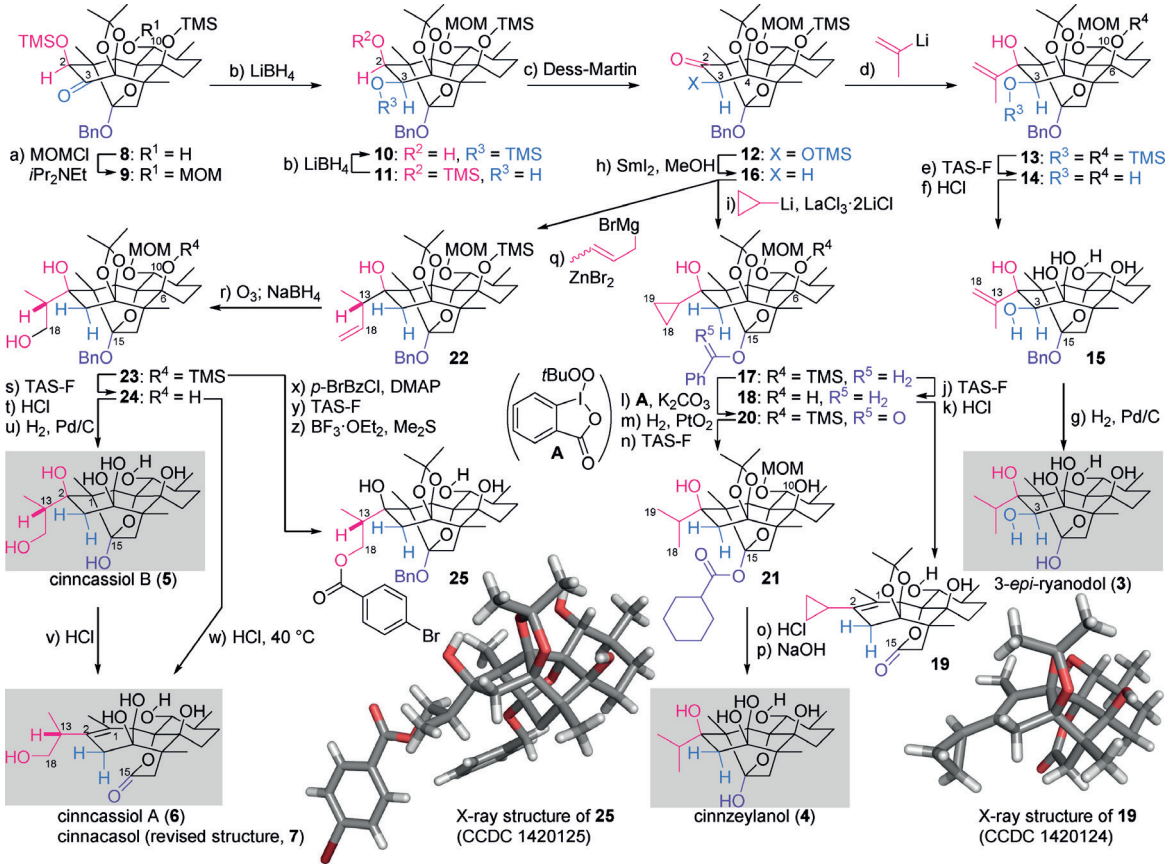
diversification at the C2,C3-positions from the common intermediate **8** and unified total syntheses of the four structurally distinct diterpenoids, 3-*epi*-ryanodol (**3**), cinnzeylanol (**4**), and cinncassiols B (**5**) and A (**6**). Furthermore, this endeavor permitted us to determine the C13*S* stereochemistry of **5**–**7**, and to correct the structures of natural ryanodol (**2**) and cinnacasol (**7**) to be those of **3** and **6**, respectively, for the first time.[16]

Along with the natural products **4**, **5**, and **6**, 3-*epi*-ryanodol (**3**) was selected as a target molecule (Scheme 1), because we assumed **3** to be the true structure of naturally occurring ryanodol (**2**). The ^{1}H and ^{13}C NMR spectra of the naturally occurring[6] and our synthetic ryanodols[15] were dissimilar, and the discrepancy with the NMR peaks resided around the C3-position, thus indicating incorrect assignment of the C3 stereochemistry.[17] The three ryanodane structures **3**–**5** would be constructed from **8** by systematic manipulations at the C2- and C3-positions. Acid treatment of **5** would promote dehydrative C–C bond cleavage to generate **6**.[4b,8] The C15-lactone reorganization from **6** was planned to build **7**, but was not performed, as the structure of cinnacasol turned out to be that of **6**, and not **7** (see below). The challenging conversions envisioned here needed to be realized at sterically congested positions, surrounded by fused rings, without damaging the preexisting functional groups. Not surprisingly, we encountered significant difficulties in attempting to translate the results of one intermediate into another laden with different functionalities, and distinct sequences were thus devised to access **3**, **4**, and **5**.

The total synthesis of 3-*epi*-ryanodol (**3**) was attained from racemic **8** in seven steps by introduction of the C2,C3-vicinal stereocenters through exploiting the acetonide group as the stereocontrolling element (Scheme 2).[18] Protection of the C10 hydroxy group of **8** as the methoxymethyl (MOM) ether yielded **9**. $LiBH_4$ induced the stereoselective reduction of the ketone at C3 of **9** from the opposite face of the acetonide-protected diol. In this event, migration of the trimethylsilyl (TMS) group occurred in situ to give the C3 TMS ether **10**,



Scheme 2. Total syntheses of 3-*epi*-ryanodol, cinnzeylanol, and cinncassiols A and B. Reagents and conditions:[30] a) $MeOCH_2Cl$ (MOMCl), NaI, iPr_2NEt, $(MeOCH_2)_2$, 80 °C; b) $LiBH_4$, tetrahydrofuran (THF), RT, **10**: 70% (2 steps), **11**: 29% (2 steps); c) Dess–Martin reagent, CH_2Cl_2, RT; d) 2-bromopropene, *t*BuLi, THF, −78 to −55 °C, 93% (2 steps); e) tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F), *N*,*N*-dimethylformamide (DMF), RT; f) 0.5 M HCl in EtOAc/MeOH (1:1), 40 °C; g) H_2, Pd/C, MeOH, RT, 73% (3 steps); h) SmI_2, MeOH, THF, RT, 93% (2 steps); i) bromocyclopropane, *t*BuLi, $LaCl_3$·2 LiCl, THF, −78 to −30 °C, 92%; j) TAS-F, DMF, RT; k) 0.5 M HCl in EtOAc/MeOH (1:1), 40 °C, 78% (2 steps); l) **A**, K_2CO_3, benzene, RT, 88%; m) H_2, PtO_2, AcOH, RT; n) TAS-F, DMF, RT; o) 0.5 M HCl in EtOAc/MeOH (1:1), RT; p) 0.25 M NaOH in H_2O/MeOH (1:4), RT, 56% (4 steps); q) MeCH=CHCH$_2$MgBr, $ZnBr_2$, Et_2O, −78 to −40 °C, **22**: 74%, the C13-epimer: 20%; r) O_3, CH_2Cl_2, MeOH, −78 °C; $NaBH_4$, RT; 3 M aqueous KHF_2, MeOH, RT, 91%; s) TAS-F, DMF, RT; t) 0.5 M HCl in EtOAc/MeOH (1:1), RT; u) H_2, Pd/C, MeOH, RT, **5**: 59% (3 steps), **6**: 30% (3 steps); v) 0.5 M HCl in EtOAc/MeOH (1:1), RT, 100%; w) 0.5 M HCl in EtOAc/MeOH (1:1), 40 °C, 94% (2 steps); x) *p*-bromobenzoyl chloride, *N*,*N*-dimethyl-4-aminopyridine (DMAP), CH_2Cl_2, RT, 94%; y) TAS-F, DMF, RT, 99%; z) BF_3·OEt_2, Me_2S, CH_2Cl_2, −78 °C, 90%.

and the remaining minor C2 TMS ether **11** was resubmitted to the same conditions for its conversion into **10**. Dess–Martin oxidation[19] of the thus liberated C2 hydroxy group of **10** gave rise to α-hydroxy ketone **12**. Addition, from the bottom face, of isopropenyl lithium to the C2 ketone of **12** introduced the correct C2 stereocenter, thus leading to **13**. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F)[20] removed the TMS groups at the C3 and C6 OH groups of **13** to produce **14**, which upon treatment with HCl in MeOH resulted in cleavage of the acetonide and C10 MOM groups to furnish the hexaol **15**. Lastly, hydrogenation of the C13 olefin and hydrogenolysis of the C15 benzyl ether transformed **15** into **3**. In accordance with our assumption, synthetic **3** was determined to match the naturally occurring ryanodol in all respects. Hence, we verified that the originally proposed structure of the natural ryanodol (**2**) was in error, and that 3-*epi*-ryanodol (**3**) represents the real structure.

The intermediate **12** was employed for the total synthesis of cinnzeylanol (**4**), that is, 3-deoxy-ryanodol. First, the OTMS group at C3 of **12** was successfully removed by using SmI_2 and MeOH to produce **16**.[21] β-Elimination of the C4 oxygen functionality from the reductively formed C2 enolate did not occur, presumably because of the rigid and stable acetonide-protected ring system. In principle, derivatization of the C3 deoxygenated **16** to the target **4** would be possible by emulating the sequence from **12** to **3**. However, nucleophilic attack of isopropenyl lithium on the C2 ketone of **16** met with failure because of the facile deprotonation (enolate formation) at C3. To decrease the basicity and increase the nucleophilicity, $LaCl_3{\cdot}2\,LiCl$[22] was utilized in combination with isopropenyl lithium, thus resulting in formation of the desired adduct, albeit in low yield (10%). After screening various nucleophiles, a reagent mixture of cyclopropyllithium and $LaCl_3{\cdot}2\,LiCl$ was found to promote the high-yielding C–C bond formation from **16**. As a result, the tetrasubstituted C2 stereocenter was correctly constructed to provide **17**. The stepwise deprotection of **17** was next attempted. Whereas TAS-F smoothly removed the TMS group at C6–OH in **17**, treatment of the obtained **18** with acidic MeOH induced not only cleavage of the MOM group at C10, but also ring-opening to afford **19**. The degraded structure of **19** was established by X-ray crystallographic analysis.

The protonated intermediate **18A**, which originated from **18**, underwent dehydrative Grob-type fragmentation into **19** by scission of the C2–O and C1–C15 bonds (Figure 1).[4b,23,24] Intriguingly, application of the same acidic conditions to **14** provided **15** while retaining the ring system. The facile fragmentation from **14** and **18** would be both feasible, when the C13–C18 bonds of the reactive intermediates **14A** and **18A** are orthogonal and parallel, respectively, to the C2–O bond. Thus, inertness of **14** is attributable to the extra C3 hydroxy group: hydrogen bonding between the C2 and C3 OH groups stabilize the structure of **14A** and decrease the basicity of the C2–OH. Alternatively, the more basic C2–OH and electron-donating σ-bond of the cyclopropyl group[25] of **18** cooperatively accelerate the dehydration by effective formation of the protonated **18A**. The C2–OH bond cleavage from **18** was indeed not prevented by extensive modification of the conditions.

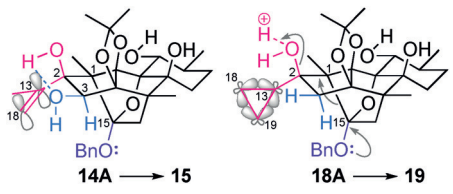


Figure 1. Rationale of facile Grob-type fragmentation of **18**.

To decelerate the undesired fragmentation, we designed the alternative substrate **21** (Scheme 2), in which both the C2-isopropyl and C15-acyloxy groups were expected to reduce electron-donating properties. First, the benzyl ether of **17** was chemoselectively converted into the benzoyl ester of **20**. Significantly, the reagent system of the hypervalent iodine(III) reagent **A** and K_2CO_3[26] oxidized the benzylic C–H bonds in the presence of many potentially reactive C–H bonds within **17**, thus leading to **20**.[27] When **20** was treated with PtO_2 under an H_2 atmosphere, reductive cleavage of the C18–C19 bond and conversion of the phenyl group into the cyclohexyl group proceeded simultaneously. The obtained compound was subjected to TAS-F to yield the diol **21** by deprotection of the C6–OTMS group. As expected, **21** proved to be considerably more stable than **18** towards the acidic conditions. The acid-mediated removal of the acetonide and MOM groups, followed by basic hydrolysis of the acyl group (C15), transformed **21** into the targeted cinnzeylanol (**4**) with no fragmentation.

Cinncassiols B (**5**) and A (**6**), the target molecules, correspond to 18-hydroxy-cinnezylanol and its Grob-fragmentation product, respectively. A prerequisite to attaining the target molecules was addition of a surrogate of the C18-hydroxy isopropyl group to the highly enolizable C2 ketone of **16**. By exploring potential surrogates, crotyl magnesium bromide was found to serve as a potent nucleophile. Treatment of **16** with crotyl magnesium bromide in the presence of $ZnBr_2$[28] resulted in formation of **22** along with the minor C13 epimer. Ozonolysis and reductive work-up with $NaBH_4$ in turn converted the C18 olefin of **22** into the C18 hydroxy group of **23**. At this stage, the C13 stereochemistry of the hydroxy isopropyl group of **23** was unambiguously determined to be *S* configured by X-ray crystallographic analysis of the C18-*p*-bromobenzoate **25**, which was derivatized from **23** in three steps. Deprotection of **23** completed the synthesis of **5**. The TMS group of **23** was removed using TAS-F to form the triol **24**. Next, acidic removal of the acetonide and MOM groups of **24** and subsequent hydrogenolysis of the benzyl ether delivered cinncassiol B (**5**) together with a small amount of cinncassiol A (**6**). Concomitant formation of **6** again validated the higher reactivity of benzyl-protected **24** than the acyl-protected **21** towards the dehydration. The compound **6** was selectively generated in high yield from **5** or more directly from **24** by HCl treatment. The NMR spectral data of synthetic **5**/**6** completely agreed with those of the authentic cinncassiol B/A. Therefore, we accomplished the first total syntheses of **5** and **6**, and assigned the hitherto unknown C13 stereochemistry to be *S*.

Close inspection of the physical data of synthetic **6** allowed us to determine that they were identical with those

of cinnacasol (**7**). Apart from this decisive evidence on its erroneous structure, **7** itself appeared to contain a highly improbable seven-membered structure, in which the C6–C11 bond adopts the *anti* conformation (Figure 2). The unusually strained character of **7** in comparison to **6** was further supported by DFT calculations of **6** and **7** at the M06-2X/6+31G(d) level of theory.[29] Namely, the most stable conformation of **7** was calculated to contain the unusually distorted tetrasubstituted carbon atom at C11, and to be 95.7 kcal mol^{-1} higher in energy than that of **6**. Taking these data together, it became clear that the structure of cinnacasol must be corrected to that of cinncassiol A (**6**) with the C13*S* stereochemistry.

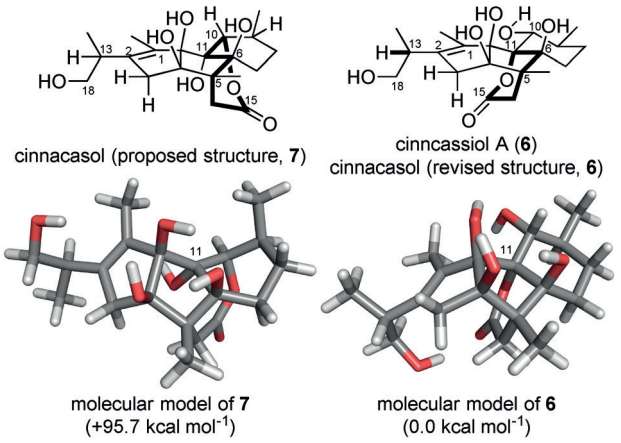


Figure 2. Proposed and revised structures of cinnacasol and their calculated stabilities.

In summary, we accomplished the concise and unified total syntheses of the four ryanodane diterpenoids from the common pentacycle **8** [3-*epi*-ryanodol (**3**; 7 steps), cinnzeylanol (**4**; 10 steps), cinncassiol B (**5**; 9 steps), and cinncassiol A (**6**; 8 steps)], and the structural revisions of the proposed structures of the two natural products [natural ryanodol (**2** to **3**) and cinnacasol (**7** to **6**)]. Furthermore, these syntheses uncovered the *S* stereochemistry at C13 of **5**, **6**, and **7**. Highly chemo- and stereoselective transformations were judiciously ordered and optimized to control the intrinsic reactivities and stereochemical biases of the highly complex pentacyclic intermediates. Such reactions include the following: a) $LiBH_4$-promoted C3 reduction and migration of the TMS group (**9**→**10**); b) SmI_2-mediated reductive elimination of TMS-oxy group at C3 (**12**→**16**); c) chemoselective benzylic C–H oxidation with hypervalent iodine(III) reagent **A** (**17**→**20**); and d) installations of the three different carbon chains at C2 from the opposite face of the acetonide group (**12**→**13**, **16**→**17**, and **16**→**22**). In addition, tuning of the reaction rates of the acid-promoted Grob-type fragmentation of **14**, **21**, and **24** significantly contributed to the success of the total syntheses. The new synthetic strategy developed here will accelerate the divergent total syntheses and detailed biological studies of natural and artificial ryanodane diterpenoids for investigating their various biological functions and enhancing their therapeutic activities.

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[30] CCDC 1420124 (**19**) and 1420125 (**25**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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