Natural Product Synthesis

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Coupling of Sterically Hindered Trisubstituted Olefins and Benzocyclobutenones by C–C Activation: Total Synthesis and Structural Revision of Cycloinumakiol**

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Abstract: *The first total syntheses of the proposed structure of cycloinumakiol (**1**) and its C5 epimer (**18**) are achieved in a concise and efficient fashion. Starting from the known 3-hydroxybenzocyclobutenone, **1** and **18** are obtained in nine and five steps with overall yields of 15% and 33%, respectively. The key for the success of this approach is the use of a catalytic C–C activation strategy for constructing the tetracyclic core of **1** through carboacylation of a sterically hindered trisubstituted olefin with benzocyclobutenone. In addition, the structure of the natural cycloinumakiol was reassigned to 19-hydroxytotarol (**7**) through X-ray diffraction analysis. This work demonstrates the potential of C–C activation for streamlining complex natural product synthesis.*

Podocarpaceae[1] is one of the most abundant evergreen trees distributed from Australia to the tropical and subtropical areas of Asia. Previous biological studies of the extracts from the leaves of this plant revealed high antibiotic as well as anticancer activities resulting from inumakiols,[1a] totarols,[1b] and other norditerpenes (Figure 1).[1c,d] Recently, guided by a bioassay based on activator protein-1 (AP-1), the investigation on extracts of *podocarpus latifolius* at the National Cancer Institute (NCI) led to the isolation of three new inumakiol-family diterpenes, namely cycloinumakiol (**1**), inumakal (**2**), and inumakoic acid (**3**).[2] The proposed structure of cycloinumakiol (**1**) is clearly different from the rest of the tricyclic inumakiol-family members. First, its oxygen substituent on the aromatic ring is *para* instead of *meta* or *ortho* to the isopropyl group; second, the oxidation and etherification of the angular C20 methyl group feature an unusual tetracyclic ring skeleton, along with an all-carbon quaternary stereocenter at the C10 position. Thus, the unique structure of **1** as well as the perhaps even more intriguing question of how cycloinumakiol is produced in nature, makes cycloinumakiol an attractive target for synthesis. Although a number of synthetic efforts have been carried out toward totarol-type diterpenes,[1b,3] to the best of our knowledge, no total synthesis was reported previously for cycloinumakiol (nor any other inumakiol family members). In this communication, we describe the development of a novel strategy for the first total synthesis of the proposed structure of cycloinumakiol and its C5 epimer, and disclose a structural revision of this natural product.

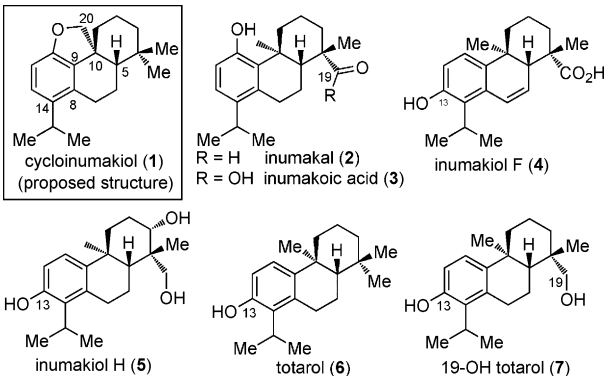
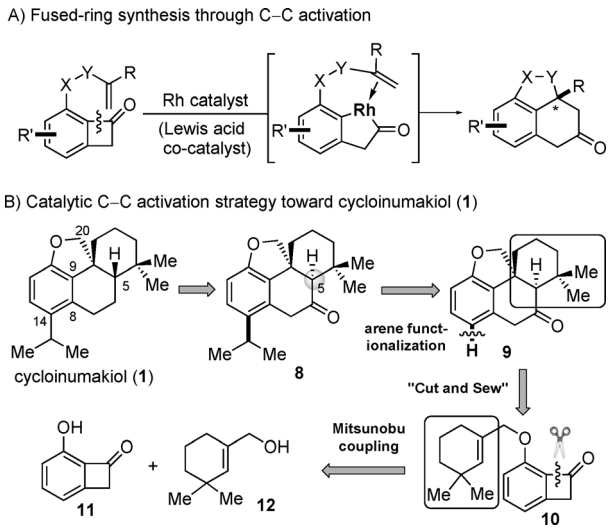


Figure 1. Representative natural products from podocarpaceae.

Our laboratory recently developed rhodium-catalyzed olefin and alkyne carboacylation methodologies through C–C activation of benzocyclobutenones (Scheme 1 A).[4,5] This intramolecular "cut and sew" sequence allows for rapid access to fused-ring skeletons from relatively simple starting materials. We anticipate that the proposed cycloinumakiol (**1**)



Scheme 1. Synthetic strategy design.

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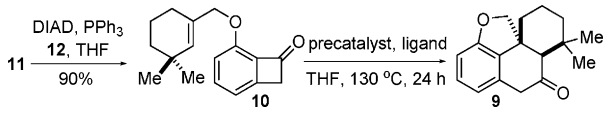
structure would provide an ideal platform to examine the applicability of this strategy for complex molecule synthesis. From a retrosynthetic viewpoint (Scheme 1 B), we envisioned that cycloinumakiol (**1**) could be accessed through stereoepimerization at the C5 position and ketone reduction from *cis*-terpenone **8**. Compound **8** would be derived from a chemo- and site-selective arene functionalization of ketone **9** that can potentially serve as a common intermediate for preparing cycloinumakiol analogues/derivatives. The tetracyclic core structure of **9** is expected to be rapidly constructed from benzocyclobutenone **10** through a catalytic intramolecular carboacylation of a hindered trisubstituted olefin. A Mitsunobu coupling of 3-hydroxybenzocyclobutenone (**11**)[6] and the known allyl alcohol **12**[7] would afford compound **10**.

The proposed synthetic approach is attractive, because it would be the first time that a catalytic carboacylation of alkenes is employed as the key step in constructing natural product skeletons,[8] allowing for an investigation of whether a C–C activation strategy can streamline the synthesis of complex molecules. However, the difficulty of the proposed approach is the employment of sterically hindered trisubstituted olefins as the coupling partner for the Rh-catalyzed carboacylation reaction. It is known that trisubstituted alkenes are highly challenging substrates for metal-catalyzed cycloaddition reactions,[9] because they generally have a much lower binding affinity for transition metals than terminal olefins.[10] We recently discovered that, assisted by a Lewis acid cocatalyst, the 1-cyclohexenyl group can undergo an intramolecular carboacylation to form polyfused rings.[4a,11,12] However, the proposed total synthesis requires the insertion of an even more sterically hindered trisubstituted olefin moiety that contains adjacent *gem*-dimethyl groups (i.e. compound **10**). Thus, we hypothesized that a more active catalyst system is needed to furnish the proposed transformation.

Substrate **10** was prepared in 90% yield through a Mitsunobu coupling between phenol **11** and allyl alcohol **12**, both of which can be prepared in three steps from commercially available starting materials.[6,7] Under the previously optimized conditions ($[Rh(cod)Cl]_2$/DPPB combination) for insertion of regular olefins,[4a] no desired product was observed (Table 1, entry 1), and addition of $ZnCl_2$ led to undesired deallylation (entry 2). The use of common ligands such as PPh_3 and DPPF gave low conversions (entries 3 and 4). In contrast, the use of more electron-rich phosphine ligands (e.g. PCy_3) resulted in significant decomposition of the starting material and more deallylation products (entry 5). While cationic Rh species were not effective (entries 6 and 7), the use of an electron-deficient Rh precatalyst was found to be critical for this transformation: the desired tetracycle **9** was isolated in 22% yield when 5 mol% $[Rh(CO)_2Cl]_2$ was employed (entry 8). Excess of CO ligand was found to be detrimental (entry 9). It was interesting to observe that electron-deficient cobalt complexes, such as $Co_2(CO)_8$, can also afford the desired product, albeit in a lower yield (entry 10). Furthermore, we found that the use of π-acidic phosphine ligands was able to enhance the turnover of the Rh catalyst (entries 13–15). Finally, tetracycle **9** can be consistently isolated in 64–66% yield[13] by utilizing a 1:2 ratio of $[Rh(CO)_2Cl]_2$ and $P(C_6F_5)_3$ (Rh:P = 1:1) as the catalyst, which was added in two portions to achieve optimal efficiency (entry 15). Delightfully, the $[Rh(CO)_2Cl]_2/P(C_6F_5)_3$ catalyst combination can also be extended to other substrates containing a cyclic and acyclic trisubstituted olefin (Figure 2).[14] Under slightly modified conditions, tri- and tetracyclic compounds **9a–c** were isolated in synthetically useful yields.

With the cycloinumakiol core structure in hand (compound **9**), we next set forth to introduce the isopropyl group at the C14 position through a site-selective arene functionaliza-

Table 1: Selected condition optimization for the key step.[a]



Entry	Precatalyst	Ligand	Conv. [%]	Yield of **9** [%][b]
1[c]	$[Rh(cod)Cl]_2$	DPPB	5	–
2	$[Rh(cod)Cl]_2$	DPPB[d]	10	–[i]
3[c]	$[Rh(cod)Cl]_2$	DPPF	< 5	–
4[c]	$Rh(PPh_3)_3Cl$[f]	PPh_3	< 5	–
5[c]	$[Rh(C_2H_4)_2Cl]_2$	PCy_3[e]	100	–[j]
6	$[Rh(acn)_2(cod)]BF_4$	none	< 5	–
7	$[Rh(cod)_2]BF_4$	none	< 5	–
8	$[Rh(CO)_2Cl]_2$	none	40	22
9	$[Rh(CO)_2Cl]_2$	5 atm CO	< 5	–
10	$Co_2(CO)_8$[g]	none	48	6.4
11	$CpCo(PPh_3)_3$[f]	none	< 5	–
12	$Rh(CO)_2acac$[f]	none	< 5	–
13	**$[Rh(CO)_2Cl]_2$[f]**	**$P(C_6F_5)_3$**	**100**	**66**
14[h]	$[Rh(CO)_2Cl]_2$	$P[3,5\text{-}(CF_3)_2C_6H_3]_3$	94	44
15[h]	**$[Rh(CO)_2Cl]_2$**	**$P(C_6F_5)_3$**	**100**	**64**

[a] Reaction conditions: Rh dimer precatalyst (5 mol%), bidentate phosphine ligand (12 mol%) or monodentate phosphine ligand (20 mol%), in THF at 130°C for 24 h. [b] Yield of the isolated product; the conversion was determined based on recycled **10**. [c] Toluene was used as solvent. [d] $ZnCl_2$ (10 mol%) was added as an additive. [e] $AgBF_4$ (10 mol%) was added as an additive. [f] 10 mol% catalyst was used. [g] of $Co_2(CO)_8$ (1 equiv) was used. [h] $[Rh(CO)_2Cl]_2$ (2.5 mol%) and $P(C_6F_5)_3$ (5 mol%) were added initially; the reaction mixture was stirred at 140°C for 12 h before another portion of the same catalyst was added. [i] Compound **11** was obtained in 10% yield. [j] Compound **11** was obtained in 20% yield. DIAD = diisopropyl azodicarboxylate, DPPB = 1,1-bis(diphenylphosphino)butane, DPPF = 1,1-bis(diphenylphosphino)ferrocene, PCy_3 = tricyclohexylphosphine.

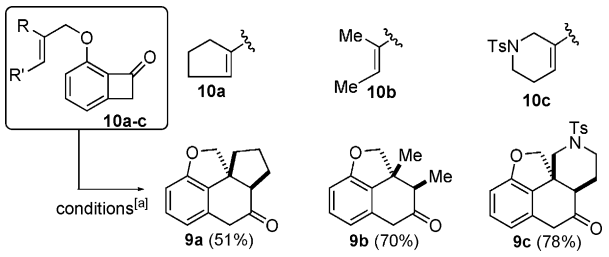
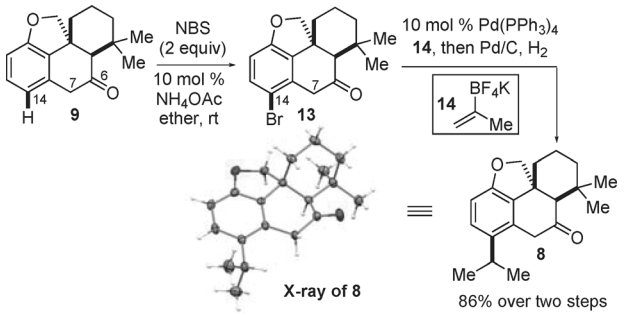


Figure 2. Carboacylation with other substrates containing trisubstituted olefins. [a] 5 mol% $[Rh(CO)_2Cl]_2$, 40 mol% $P(C_6F_5)_3$, in THF at 130°C for 36 h.

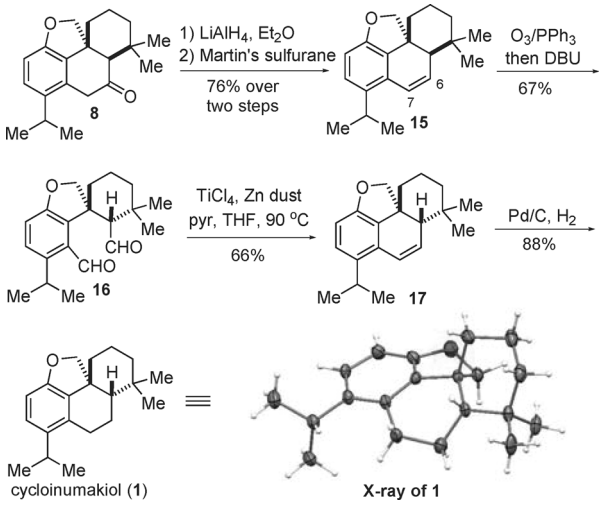
tion (Scheme 2). To our delight, treatment of **9** with NBS (2 equiv) and a catalytic amount of NH_4OAc[15] at room temperature led to a highly site-specific bromination in a near quantitative yield. Note that the activated C7 position remained intact under the oxidative conditions. A one-pot sequence of Suzuki cross-coupling with vinyl trifluoroborate salt **14**[16] and hydrogenation furnished *cis*-terpenone **8** in 86% overall yield from core compound **9**.



Scheme 2. Chemo- and site-selective arene functionalization.

We next attempted to directly invert the C5 stereocenter of compounds **9** and **8**. However, under either strong basic or acidic conditions no epimerization was observed, which is likely due to the rigid nature of the tetracyclic skeleton causing a high kinetic barrier (e.g. torsional strain by the angularly fused hydrofuran ring).[17] Nevertheless, we found a three-step sequence was effective to completely invert the C5 stereocenter (Scheme 3). The ketone was first converted to an olefin in high yields by $LiAlH_4$ reduction and dehydration; ozonolysis/reduction followed by in situ treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded dialdehyde **16** in the correct diastereomeric form. Subsequently, we took advantage of the McMurry coupling and restored the C6-C7 olefin.

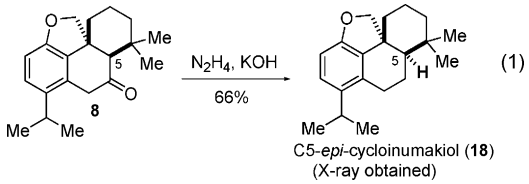
Finally, hydrogenation of alkene **17** provided the proposed cycloinumakiol (**1**) in 88% yield, the structure of which



Scheme 3. Synthetic sequence.

was unambiguously confirmed by $^1H/^{13}C$ NMR spectroscopy, HRMS, IR spectroscopy, and X-ray crystallography. While we are confident about our structural characterization of **1**, unfortunately, the NMR spectra of synthetic cycloinumakiol do not match those reported in literature.[2] Thus, we anticipated there was a structural misassignment for cycloinumakiol.

To examine whether the natural product is the other diastereomer of **1**, we performed a Wolff–Kishner reduction of ketone **8** and obtained the C5-*epi*-cycloinumakiol **18** [Eq. (1)]. The structure of **18** was also unambiguously



confirmed by $^1H/^{13}C$ NMR spectroscopy, HRMS, IR spectroscopy, and X-ray crystallography. Again, the NMR spectra of **18** do not match the reported data of cycloinumakiol.[2] After careful analysis and comparison between ours and reported ^1H NMR data, we found a significant difference in chemical shifts of the C20-methylene group: those of the natural sample are at 3.78 and 3.42 ppm, whereas those of the synthetic samples **1** and **18** are around 4.6 and 4.1 ppm, respectively. Based on our previous experience on preparing benzohydrofuran compounds,[4] we suspected that the natural cycloinumakiol likely does not contain a benzohydrofuran motif.

Toward this end, thanks to a generous donation of the natural cycloinumakiol sample (ca. 0.5 mg) from the NCI, we were able to further purify the sample, and gratifyingly, obtained a single crystal of this compound. X-ray crystallography analysis eventually revealed that the natural cycloinumakiol has the same structure as 19-hydroxytotarol (Figure 3).[18]

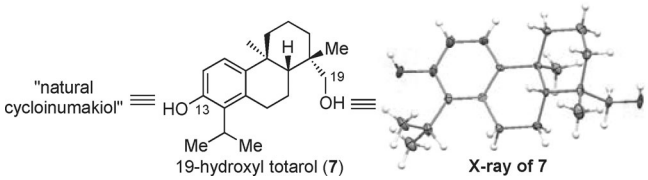


Figure 3. Structure elucidation of the natural cycloinumakiol.

In conclusion, we accomplished the first total syntheses of the proposed structure of cycloinumakiol (**1**) and its C5 epimer (**18**). This strategy features a Rh-catalyzed intramolecular coupling of a sterically hindered trisubstituted olefin with a benzocyclobutenone. Neither the synthesis of **1** nor **18** employed any protecting group. The conciseness of the total synthesis demonstrates that the "cut and sew" transformation can serve as a useful strategy to prepare structural motifs of high complexity, which is complementary to classical cycloaddition reactions. Furthermore, motivated

by these synthetic endeavors, the structure of the natural cycloinumakiol was re-examined and revised as 19-hydroxytotarol (**7**), suggesting that chemical synthesis still plays an important role in validating the structure of natural products.[19] Investigation of the biological activity of the synthetic cycloinumakiol (**1**), the C5 epimer (**18**), and other intermediates is ongoing in collaboration with other groups.

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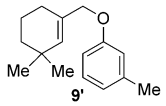
[13] Around 5 % yield of the decarbonylation product **9′** was isolated as the major byproduct.



9'

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[20] CCDC 999131 (**1**), 99729 (**8**), 997288 (**18**), and 997289 (**7**) 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.