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# Total Syntheses of (±)-Melicolones A and B

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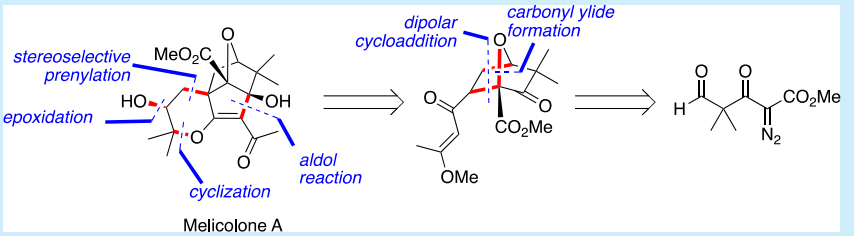


**ABSTRACT:** The first total syntheses of (±)-melicolones A and B, which have a unique and densely functionalized framework derived from a rearranged prenylated acetophenone, were accomplished in 12.3% combined overall yield. The concise and divergent synthesis of these two natural products, which were isolated in racemic form, was achieved in a longest linear sequence requiring only 9 steps (11 total steps) and 8 isolated intermediates using commercially available starting materials. This approach, which might enable access to all tetracyclic melicolones, features the highly regioselective (16:1) and diastereoselective (15:1) dipolar cycloaddition of a carbonyl ylide generated by the unusual cyclization of a rhodium carbene with the carbonyl oxygen atom of an aliphatic aldehyde. This cycloaddition proceeds with dominant steric control to give a highly functionalized oxabicycloheptane core. Stereoselective enolate alkylation led to a prenylated intermediate that underwent an intramolecular aldol reaction to give the penultimate tricyclic intermediate. Tandem epoxidation of the pendant prenyl group followed by a regioselective, acid-catalyzed cyclization delivered (±)-melicolones A and B.



Melicolone A (**1**) and melicolone B (**2**) are epimeric natural products with an unprecedented 9-oxatricyclo [3.2.1.1$^{3,8}$] nonane core that is derived from a prenylated rearranged acetophenone. These unique compounds were isolated in 2015 as racemates from the leaves of *Melicope ptelefolia*, a deciduous shrub distributed in Southeast Asia, by Kong and coworkers (Figure 1).[1] Interest in the molecular components found in many species of *Melicope* owes its origin to a long history of their use in folk medicines.[2] Indeed, both enantiomers of **1** and **2** show potent cell protecting activities against high glucose-induced oxidative stress in human vein endothelial cells, suggesting they might be potential leads to treat diabetic endothelial dysfunction. Since their discovery, a number of other melicolones have been isolated, including several having the same tetracyclic skeleton, as exemplified by melicolones H (**3**), J (**4**), G (**5**), and I (**6**).[3]

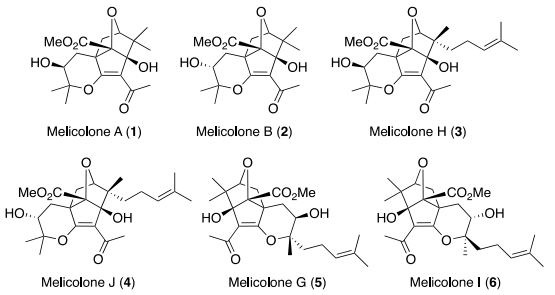


**Figure 1.** Structures of representative tetracyclic melicolones.

The remarkable structures of the diastereomeric melicolones A and B (**1** and **2**) coupled with their promising biological activity inspired us to develop a concise approach for their synthesis that might be applied to the preparation of other melicolones having a bridged oxabicycloheptane core. The plan features the novel intermolecular dipolar cycloaddition of the cyclic carbonyl ylide **10**, which is generated in situ by the rhodium(II)-catalyzed cyclization of the diazo compound **11**, with **9** to give the oxabicycloheptane **8** (Scheme 1). Cycloadditions of such carbonyl ylides are well-known,[4,5] but these intermediates are generally formed by cyclization of a metallocarbene with the carbonyl oxygen atom of a ketone, ester, or amide; examples involving an aliphatic aldehyde are rare.[6] Another unusual aspect of the proposed cycloaddition of **9** and **10** is that the regiochemical outcome required to access **1** and **2** is opposite that expected based upon the usual electronic effects; however, we reasoned that steric effects would dominate this reaction to give **8** as the preferred

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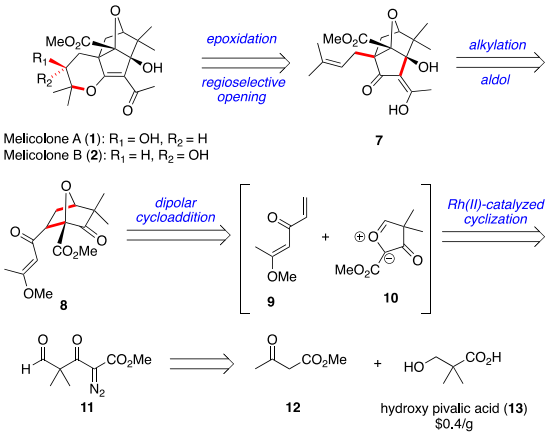
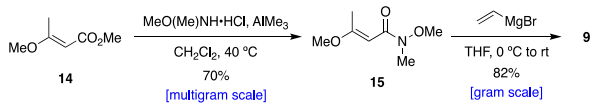
**Scheme 1. Retrosynthetic Analysis of Melicolone A and B**



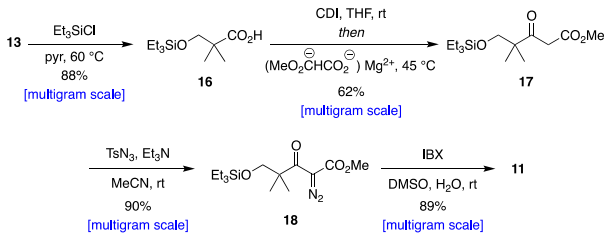

product. We further envisioned that **9** and **11** would be readily accessible from the inexpensive starting materials **12** and **13**, respectively. Stereoselective prenylation of **8** then sets the stage for an aldol cyclization to give **7**, epoxidation and acid-catalyzed cyclization of which will deliver a mixture of racemic **1** and **2**.

Toward the pivotal carbonyl ylide cycloaddition, the requisite starting materials **9** and **11** were prepared in a straightforward fashion according to Schemes 2 and 3,

**Scheme 2. Synthesis of Unsaturated Vinylogous Ester 9**



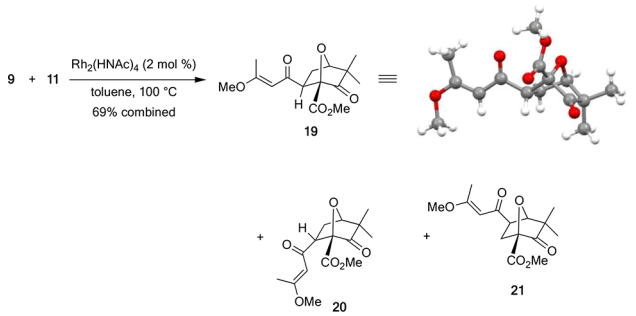

**Scheme 3. Synthesis of α-Diazo Ester 11**




respectively. The known vinylogous carbonate **14**, which though commercially available, was readily prepared from inexpensive methyl acetoacetate [$CH(OMe)_3$, cat. $H_2SO_4$; 85%],[7] was converted into **9** via the Weinreb amide **15** in 57% overall yield (Scheme 2). Toward **11**, the hydroxyl group of hydroxypivalic acid (**13**) was first protected to give **16**. The acid moiety of **16** was then modified by activation with carbonyldiimidazole (CDI) followed by a crossed-Claisen reaction with the dianion of monomethyl malonate to provide the keto ester **17** as an inconsequential mixture (3.5:1) of keto−enol tautomers in 55% overall yield (Scheme 3). Subjection of **17** to diazotransfer followed by direct oxidation of the silyl protected alcohol **18** with iodoxybenzoic acid (IBX)[8] furnished **11** in 80% overall yield.

The pivotal, rhodium(II)-catalyzed, carbonyl ylide cycloaddition was at hand. In an initial experiment, we were gratified to discover that heating **9** and **11** in toluene in the presence of 2 mol % $Rh_2(OAc)_4$ was regioselective and gave a mixture of three isomeric cycloadducts **19**−**21** in 37, 10, and 7% yields, respectively (Scheme 4). The structures of these compounds were initially assigned based upon 2D NMR experiments, but

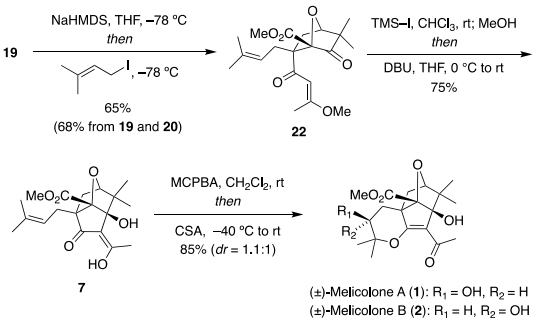
**Scheme 4. Rhodium(II)-Catalyzed Cycloaddition**




the structure of **19** was unambiguously determined by X-ray crystallography.[9] After some experimentation, we discovered that when 2 mol % $Rh_2(HNAc)_4$ was employed as the catalyst, the cycloaddition was even more efficient and regioselective (16:1) and furnished **19** in 61% isolated yield together with the epimer **20** (4%) and the regioisomeric adduct **21** (4%). Our original expectation that the regiochemical course of the cycloaddition would be dominated by steric effects imposed by the neopentyl center in the carbonyl ylide **10** was justified. The high stereoselectivity of this reaction is rendered moot in the subsequent enolate alkylation step, but it is also notable that the cycloaddition proceeds with high exoselectivity (dr = 15:1), presumably because the *endo*-transition state is sterically more hindered by the presence of the *endo*-methyl group of the *gem*-dimethyl moiety. Although melicolones A and B occur in nature as racemates, we briefly explored the use of chiral rhodium catalysts to induce an enantioselective cycloaddition,[6a,b] but the enantioselectivities using known catalysts were low.

Inasmuch as the cycloadducts **19** and **20** were isolated in pure form by chromatography, they were advanced separately in the next step. Stereoselective prenylation from the sterically more accessible *exo*-face of the enolate generated from **19** proceeded without detectable *β*-elimination[10] of the bridging oxygen atom to provide **22** in 65% yield (Scheme 5).

**Scheme 5. Synthesis of Melicolones A and B**




Prenylation of **20** under identical conditions furnished **22** in the same yield, so the overall yield of **22** from **19** and **20** was 68%. Selective removal of the methyl ether group of **22** with iodotrimethylsilane (TMS-I) produced an intermediate enol that was not isolated but was subjected directly to base-induced intramolecular aldol cyclization to give the penultimate tricyclic intermediate **7** in 75% yield from **22**.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Epoxidation of **7** with *m*-chloroperbenzoic acid (MCPBA) followed by regioselective acid-catalyzed cyclization[11] delivered a mixture that was separated by reverse phase HPLC to give (±)-melicolone A (**1**) and (±)-melicolone B (**2**) in 44 and 41% yields, respectively. The $^{1}$H and $^{13}$C NMR spectra of synthetic **1** and **2** are consistent with those reported for the corresponding natural products.[1]

In summary, we completed the first total syntheses of (±)-melicolone A (**1**) and (±)-melicolone B (**2**), which are compact and densely functionalized natural products derived from a rearranged prenylated acetophenone. This divergent synthesis is remarkably concise and requires only 9 steps (11 total) and 8 isolated intermediates in the longest linear sequence using commercially available starting materials. Significantly, the strategy potentially represents a unified approach to all melicolones containing a tetracyclic core. The approach features an unusual and highly regioselective (16:1) and stereoselective (15:1) dipolar cycloaddition of an unsaturated vinylogous ester with a carbonyl ylide that is generated by the cyclization of a rhodium carbene with the carbonyl oxygen atom of an aliphatic aldehyde to create the oxabicycloheptane core. A notable feature of this cycloaddition is that the regiochemical and stereochemical outcomes are dominated by steric effects rather than the more commonly observed electronic ones. Stereoselective prenylation of each of the epimeric cycloadducts having the correct regiochemistry led to an intermediate that underwent facile intramolecular aldol reaction to furnish the penultimate tricyclic intermediate. Tandem epoxidation of the prenyl group followed by regioselective acid-catalyzed opening delivered (±)-melicolones A and B in a combined overall yield of 12.3%.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03454.

Experimental procedures, characterization data, spectral comparison of synthetic and natural melicolones A and B, and copies of $^{1}$H and $^{13}$C NMR spectra (PDF)

### Accession Codes

CCDC 1992810 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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