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Synthesis of (+)-Coronafacic Acid

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An enantioselective synthesis of (+)-coronafacic acid has been achieved. Rhodium-catalyzed cyclization of an α-diazoester provided the intermediate cyclopentanone in high enantiomeric purity. Subsequent Fe-mediated cyclocarbonylation of a derived alkenyl cyclopropane gave a bicyclic enone that then was hydrogenated and carried on to the natural product.

Introduction

Bicyclic and polycyclic ring systems are common in structurally complex and physiologically active natural products. Although there are many methods of preparing such ring systems, the number of approaches to carbopolycyclic scaffolds is more limited. Corey demonstrated the utility of an enzyme to convert 20,21-dehydro-2,3-oxidosqualene to a dehydroprosterol. Hajos2 employed a catalytic amount of (S)-(−)-proline in an asymmetric aldol condensation to form optically pure bicyclic intermediates. We3 were able to demonstrate that a single stereogenic center on the bridge between the diene and dienophile could set the absolute center of an intramolecular Diels–Alder reaction leading to a carbobicyclic 6,6-system. Corey4 reported examples of catalytic enantioselective [2 + 2] cycloaddition catalyzed by chiral aluminum bromide complexes to form 5,4-, 6,4-, and 7,4-carbocyclic systems. We5 also reported another approach to enantioselective polycyclic construction, utilizing Shi epoxidation followed by selective ring opening, and then intramolecular alkylation to set the stereogenic centers. We6 further showed in our synthesis of (+)-sulcatine G that enantiospecific C–H insertion, followed by intramolecular alkylation, could also be applied to carbobicycle construction. Schaus7 demonstrated the utility of the Morita–Baylis–Hillman reaction, coupled with the Hosomi–Sakurai reacton, to construct 6,6-bicyclic systems. Gaunt8 reported a strategy using oxidative dearomatization and amine-catalyzed enantioselective desymmetrizing Michael reaction to form 6,6-carbocycles. In the Phillips9 synthesis of (+)-cyanthiwigin U, tandem metathesis was used to enantioselectively construct the polycarbocycle. Recently, Ishihara10 utilized enantioselective Robinson annulation and cycloaddition reactions catalyzed by chiral Lewis acids for polycarbocycle construction.

We had developed (Scheme 1) a general route to enantioselectively pure 5,3- and 6,3-carbocyclic scaffolds by cyclization of menthyl esters such as 1 to the cyclopentanone 2.11a Nakada11b later reported an enantioselective preparation of similar carbocyclic esters and sulfones by copper-catalyzed

asymmetric intramolecular cyclopropanation. We have improved upon our intramolecular cyclization\textsuperscript{11a} by increasing the selectivity and preparative yield of the cyclization. We anticipated that we could convert the ester to the alkenyl cyclopropane 3. We speculated\textsuperscript{12} that Fe-mediated cyclocarbonylation of the alkenyl cyclopropane could deliver the bicyclic enone 4. If this were successful, the enone 4 could then be transformed in a few steps to the natural product (+)-coronafacic acid 5.

Background and Results

Coronatin 6 (eq 1) is a phytotoxin produced by \textit{Pseudomonas syringae}. Its structure is composed of coronafacic acid 5, a bicyclic core with three stereogenic centers, and coronamic acid 7, a cyclopropane amino acid derived from isoleucine. Both coronatin and coronafacic acid have been reported to mimic jasmonic acid. All three compounds induce tubers, induce cell expansion, inhibit cell division, and promote senescence in plants.\textsuperscript{13} While there were 15 previous total syntheses of coronatin and coronafacic acid have been reported\textsuperscript{14} only one enantioselective route had been reported.\textsuperscript{14m}

Intramolecular Cyclopropanation. Dirhodium tetracarboxylate catalysts are known to cyclize \(\alpha\)-diazo esters, such as 1. We had previously cyclized 1 to a 1:1 mixture of 2 and 8 (eq 2) using a copper bronze catalyst.\textsuperscript{11a} We separated the menthyl esters 2 and 8 by column chromatography, leading to pure 8\textsuperscript{b} by preparative yield of the cyclization. We anticipated entry 2

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<th>entry</th>
<th>rhodium</th>
<th>ligand</th>
<th>solvent</th>
<th>T (°C)</th>
<th>diastereoselectivity (2:8)</th>
<th>yield (%)</th>
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<td>1.5:1</td>
<td>89</td>
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</table>

\textsuperscript{a} Yields reported are for the isolated mixture of the two diastereomers. \textsuperscript{b} See ref 15a. \textsuperscript{c} See ref 15b. \textsuperscript{d} See ref 15c. \textsuperscript{e} See ref 15d. \textsuperscript{f} See ref 15e. \textsuperscript{g} See ref 15f. \textsuperscript{h} See ref 15g. \textsuperscript{i} See ref 15h.

We have found (Table 1) that, by using Rh(II) catalysts, we could induce some diastereoselectivity in this cyclization. We found that dirhodium pivalate at room temperature provided the best preparative yield, 63%, of the desired cyclopentanone 2.

Preparation of Alkenyl Cyclopropane 6. With the initial two stereocenters set, we protected (Scheme 2) the keto as the ketal 9. Attempts to reduce the ester directly to the aldehyde with less than 1 equiv of lithium aluminum hydride or with Dibal delivered a mixture of alcohol, aldehyde, and the starting ester. We found that completely converting the ester 2 to the alcohol followed by oxidation to aldehyde 10 with Dess-Martin

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reagent was more effective. We were then able to perform a Wittig reaction on aldehyde 10 to give alkenyl cyclopropane 3.

Preparation of Enone 9. We12b previously reported the preparation of 2,5- and 5-substituted cyclohexenones via Fe-mediated cyclocarbonylation. More recently, we found that we could couple the Wittig reaction with Fe-mediated cyclocarbonylation to convert aldehydes to 2-substituted cyclohexenones.12c Sarel12a demonstrated the photochemical expansion of a methylene spiroalkane 11 to the bicyclic enones 12 and 13 in his studies of (+)-\(\alpha\)-thujene (eq 3). The cyclocarbonylation to a bicyclic enone from a 5,3- or 6,3-ring fused alkenyl cyclopropane such as 3 had not yet been reported.

We found (eq 4) that UV irradiation of 3 in the presence of Fe(CO)\(_5\), rather than 2-propanol,12b was buffered and ketal deprotection was avoided. The use of the desired unsaturated ketone. This was not purified but was converted to starting material was easily separated and recycled.

The kinetic product from the cyclocarbonylation was the \(\beta,\gamma\)-unsaturated ketone. This was not purified but was converted to the desired \(\alpha,\beta\)-unsaturated ketone 4 by stirring for 1 h at room temperature with DBU.

Synthesis of (+)-Coronafacic Acid. Pd-mediated hydrogenation of the cyclohexenone 4 (Scheme 3) at ambient temperature and pressure provided the bicyclic ketone 11 as a single diastereomer. Carbomethoxylation followed by reduction with sodium borohydride gave the alcohol 12 as a mixture of diastereomers. Dehydration of the mixture by mesylation and subsequent addition of DBU gave the ketal-protected coronafacic methyl ester 13 as a single diastereomer. Deprotection and ester hydrolysis were then completed in one step with aqueous HCl at reflux to give the natural product 5. The physical data, including optical rotation (obsd [\(\alpha\])\(_D\) +104; lit.14a [\(\alpha\])\(_D\) +105), were consistent with those previously reported for (+)-coronafacic acid.

Conclusion

We have completed an enantioselective synthesis of (+)-coronafacic acid. We were able to set the initial two stereogenic centers utilizing rhodium-catalyzed intramolecular cyclopropanation. We were then able to expand the cyclopropane utilizing Fe-mediated cyclocarbonylation. We expect that this will be a general route to enantioselectively pure 6,5- and 6,6-carboxibicyclic systems.

Experimental Section

(15,2R,5S)-5-Methyl-2-(propan-2-yl)cyclohexyl 2-Oxobicyclo[3.1.0]hexane-1-carboxylate 2 and 8. Rh\(_2\)(Piv)\(_4\) (5 mg) was added to \(\alpha\)-diazoester 11a (6.12 g, 20 mmol) in 20 mL of dry CH\(_3\)Cl (1.0 M) at rt. The solution was stirred at rt for 1 h, and then additional Rh\(_2\)(Piv)\(_4\) (5 mg) was added and the reaction allowed to stir for an additional 2 h. The mixture was concentrated and the residue chromatographed using 94:6 hexanes/EtOAc as elution solvent to give the cyclopentanone 2 (3.61 g, 63% yield) and 8 (1.78 g, 32% yield) as an oil. Cyclopentanone 2 was then crystallized at \(-78^\circ\)C in petroleum ether (5 mL) to give 2 (3.49 g, 62% as a white crystalline solid: mp = 34–36 °C; [\(\alpha\])\(_D\) +47.2 (c = 1.0, CH\(_2\)Cl\(_2\)); TLC R\(_f\) = 0.27 (9:1 hexanes/EtOAc); 1H NMR \(\delta\) 4.71 (dt, J = 4.9, 11.5 Hz, 1H), 2.54 (m, 1H), 2.22 (m, 3H), 2.01 (m, 4H), 1.68 (d, [J = 12.1 Hz, 2H]), 1.34–1.48 (m, 3H), 0.88–1.05 (m, 9H), 0.75 (d, J = 7.6 Hz, 3H); 13C NMR \(\delta\) 123.9 (1H); HRMS calcd for C\(_{11}\)H\(_{14}\)O\(_2\) (M + H)\(^+\) 179.0990, obsd 179.0991.

Rayonet apparatus (300 nm) set for autocooling. The reaction was halted every hour to agitate the tube inside the larger tube, after which photolysis was restarted. At the end of the irradiation, DBU (304 mg, 2.0 mmol) was added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was diluted with 40 mL of EtOAc and filtered through a small pad of packed silica gel. The eluate was concentrated and the residue was chromatographed to give 152 mg of unreacted 3 and 90 mg of 4 (98% yield based on 3 not recovered) as an oil: [α]D20 +102.5 (c = 1.0, CH2Cl2); TLC Rf = 0.30 (8:2 petroleum ether/MTBE); 1H NMR δ 6.45 (s, 1H), 3.45 (m, 4H), 2.95 (br s, 1H), 2.64 (m, 1H), 2.41 (m, 2H), 2.17 (m, 2H), 1.70–1.97 (m, 3H), 1.35 (m, 1H), 0.95 (m, 6H), 0.85 (m, 3H); 13C NMR δ 178.4, 170.8, 165.7, 140.7, 107.1, 122.2, 70.4, 39.9, 30.5, 29.3, 25.0, 21.7, d 138.9, 45.0, 33.1, 21.5, 21.3, 12.1; IR 2952, 1672, 1493, 1312, 1153 cm⁻¹; MS m/z 309 (M + H, 8), 279 (7), 237 (12), 222 (94), 209 (37), 165
Synthesis of (+)-Coronafacic Acid

(+)-Coronafacic Acid 5. Hydrochloric acid (20% aqueous, 2 mL) was added to ketal ester 16 (11 mg, 0.07 mmol). The mixture was heated to reflux for 4 h. The solution was allowed to cool to rt and then partitioned between water and EtOAc. The combined organic extract was dried (MgSO4) and concentrated. The residue was chromatographed to give 5 (7 mg, 55% yield) as an oil: TLC \( R_f = 0.25 \) (7:3 petroleum ether/EtOAc); [\( \alpha \)]\text{D}^20 +104 (c = 0.1, MeOH) (lit.14o [\( \alpha \)]\text{D}^20 +105). The spectroscopic data of the natural product 5 were compared with those of earlier syntheses14o and found to be identical.

Acknowledgment. We thank John Dykins for high-resolution mass spectrometry under the financial support of NSF 054177. We thank the NIH (GM060287) for financial support of this work.

Supporting Information Available: General experimental procedures, details of the photochemical apparatus, preparation of 1, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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