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Efficient route to 4*H*-1,3-oxazines through ring expansion of isoxazoles by rhodium carbenoids

James R. Manning and **Huw M. L. Davies***
Department of Chemistry, University at Buffalo, The State University of New York, Buffalo, New York, 14260-3000

Abstract

Studies related to the total synthesis of elisabethin C led to the discovery of a rhodium-catalyzed cascade sequence involving isoxazole ring expansion and a [4 + 3] cycloaddition. The scope of the isoxazole ring expansion was explored, resulting in the synthesis of a range of 4*H*-1,3-oxazines in 47–96% yield

Keywords

isoxazole ring expansion; N–O insertion; rhodium carbenoid; aryldiazoacetates

1. Introduction

The metal-catalyzed reactions of diazo compounds are capable of a diverse array of transformations.[1] With the advent of new catalysts and the recognition that different classes of carbenoids can open up new vistas of reactivity, the field continues to expand.[2] We have had a long-standing interest in developing new synthetic methods derived from the chemistry of donor/acceptor-substituted carbenoids. This paper describes the discovery of an unexpected but highly efficient ring expansion of isoxazoles by rhodium carbenoid intermediates.

A recent focus of our group has been the synthesis of biologically active marine natural products utilizing the enantiodivergent combined C–H activation/Cope rearrangement methodology.[3] This reaction occurs during allylic C–H functionalization using rhodium-stabilized vinylcarbenoids. Recent total syntheses completed using this methodology include (+)-erogorgiaene (**3**),[4] (−)-elisapterosin B (**4**),[5] and (−)-colombiasin A (**5**).[5] This strategy has been successful at rapidly introducing three of the stereocenters common in these natural products by differentiating between the enantiomers of the racemic dihydronaphthalene derivative **1**. One enantiomer of the substrate undergoes the combined C–H activation/Cope rearrangement while the other is cyclopropanated (Scheme 1).

In seeking to broaden the scope of this methodology, we focused our attention on the marine *bisnor*-diterpenoid elisabethin C (**6**),[6,7] using the fused isoxazole **8** as the substrate for the

*Corresponding author. Tel.: +1-716-645-6800x2186; fax: +1-716-645-6547; e-mail: hdavies@acsu.buffalo.edu.

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combined C–H activation/Cope rearrangement (Scheme 2). The isoxazole subunit would be used as a protecting group for the diketone functionality of elisabethin C, to be unmasked at a late stage of the synthesis.

2. Results and discussion

The synthesis of fused isoxazole **8** was achieved using a relatively straightforward approach starting from β-diketone **9**, which in turn was readily prepared by literature procedures[8,9] from the commercially available mono-protected 1,4-cyclohexadione (Scheme 3). If the isoxazole forming reaction was allowed to run to completion, the resulting regioisomeric mixture of isoxazoles proved inseparable by chromatography at all subsequent steps. Fortunately, if the reaction was stopped after 10 min, the regioisomeric oxime intermediates **10** and **11** could be chromatographically separated. Treatment of each isomer separately with warm acetic acid furnished the corresponding isoxazoles in isomerically pure form. Regioisomer **11** was chosen initially to carry through the sequence to test the key carbenoid reaction. Cyclization to form isoxazole **12** and subsequent acetal deprotection to ketone **13** proceeded smoothly. The remaining two steps to form vinyl triflate **15** using Comins' reagent **14**[10] followed by a palladium-catalyzed reduction[11] gave **8** in good overall yield.

The Rh_2(*R*-DOSP)$_4$-catalyzed reaction[12] of the fused isoxazole **8** with vinyldiazoacetate **2** (3 equiv) gave a most unusual result (Scheme 4). Instead of the expected reaction to form **7**, the major isolable product was an unprecedented tricyclic derivative **16**, which was formed as a 1 : 1 mixture of diastereomers in 62% yield. Each diastereomer was formed with low enantioinduction (19% ee). This material has incorporated into isoxazole **8** two equivalents of the vinylcarbenoid derived from **2**. Compound **16** can be considered as formally derived from a carbenoid insertion into the isoxazole N–O bond and a tandem cyclopropanation/Cope rearrangement between another carbenoid and the diene component of the substrate.

The formation of **16** is an unusual transformation and we were intrigued by this novel carbenoid reactivity. Formal [4 + 3] cycloadditions between vinylcarbenoids and dienes by a tandem cyclopropanation/Cope rearrangement are well precedented,[13] but the carbenoid insertion into the isoxazole N–O bond is not an established process. Rhodium carbenoids containing isoxazoles have been used in intermolecular cyclopropanations without any side reaction on the isoxazole ring.14 Additionally, intramolecular C–H insertion reactions have been successfully achieved on substrates containing an isoxazole ring.15 It is known, however, that isoxazolium ylides, typically generated by deprotonation of an isoxazolium salt, undergo rearrangements to generate either 4*H*-1,3-oxazines or 3-imino-2-en-1-ones, depending on the substitution of the isoxazolium salt.[16] Consequently, we decided to explore further the scope of the N–O insertion chemistry using rhodium carbenoids and various isoxazole substrates.

The first series of experiments studied the effect of the carbenoid structure on the efficiency of the N–O insertion, using 3,5-dimethylisoxazole (**18**) as a reference substrate (Table 1). In recent years we have shown that donor/acceptor-substituted carbenoids are capable of higher selectivity than the conventional carbenoids lacking a donor group. In this case all three of the prototypical types of carbenoids, derived from **17a–c**, induced an N–O insertion into the isoxazole, although the reaction with the donor/acceptor-substituted carbenoid (entry 3) was the most efficient (88% yield).

The next series of reactions were conducted to determine what types of functionality on the isoxazole would be compatible with the N–O insertion (Table 2). Methyl phenyldiazoacetate (**17c**) was used as the carbenoid source because it had resulted in the highest yield of product in the initial evaluation. Further studies were performed with a range of isoxazoles (Table 2). All four isoxazoles **20a–d** produced the 4*H*-1,3-oxazine products **21a–d**, respectively in high

yield (67–96%). These studies demonstrate that siloxy, halo and even ester functionalities are compatible with this chemistry. The ester derivative **20d** gave a tautomeric mixture of the ring expansion products **21d** and **22d** (Entry 5). Compound **21d** was formed cleanly in the carbenoid reaction, but is prone to isomerization to **22d** during silica gel chromatography, illustrating the relative mildness of the carbenoid reaction conditions.

Having discovered that isoxazoles could be effectively ring-expanded, it became of interest to determine if the reaction could be extended to other heterocyclic systems. Benzisoxazoles were found to be similarly reactive with carbenoids, although further transformations occurred in certain cases (Scheme 5). The reaction with 1,2-benzisoxazole **23** produced the ring expansion product **24** cleanly in 72% yield if **23** was used in excess, and aziridine **25** in 94% yield if 3 equiv of the diazo component was used. In the case of anthranil **26**, aldehyde **27**, formally the result of a 6π-electrocyclic ring-opening of the expected N–O insertion product, was isolated along with epoxide **28**. Compound **28** could be obtained exclusively if 3 equiv of the diazoacetate was used in the reaction. 5-Chloro-3-phenylanthranil (**29**) cleanly produced ketone **30**, which did not readily undergo epoxide formation.

Another system worthy of study was benzoisothiazoles (Scheme 6). Previously it had been shown that the related 2-substituted isothiazol-3(2*H*)-ones undergo N–S insertion with carbenoids lacking an electron-donating group.[17] The reaction of **17c** with 3-chloro[*d*] benzoisothiazole (**31**) was a very efficient process resulting in the formation of 2*H*-1,3-benzothiazine **32** in 88% yield.

The reaction mechanism for the transformations described above likely proceeds through an isoxazolium ylide intermediate **33**, formed by attack of the isoxazole nitrogen onto the rhodium carbenoid (Scheme 7). At this point, two reasonable pathways could lead to the ring-expanded product **35**. The ylide **33** could undergo a 1,2-shift to generate **35** directly, as previously proposed for the ring expansion of 2-substituted isothiazol-3(2*H*)-ones.[17] Alternatively, ylide **33** could undergo a ring opening to **34**, followed by a 6π electrocyclization to give **35** as proposed for the ring expansion of isoxazolium ylides derived from deprotonation of isoxazolium salts.[16c]

3. Conclusion

In summary, the reactions of various isoxazoles with rhodium carbenoids have been examined and found to produce 4*H*-1,3-oxazines through a ring expansion in good to excellent yields. These reactions are likely to proceed via ylide intermediates which then either expand through a 1,2-shift, or open up to 3-imino-2-en-1-ones which subsequently undergo a 6π electrocyclization to 4*H*-1,3-oxazines. Studies toward applications of this transformation in heterocycle synthesis are currently underway.

4. Experimental

4.1. General

All experiments were performed under anhydrous conditions in an atmosphere of argon except where stated, using flame dried glassware. 2,2-Dimethylbutane (DMB) was purified by distillation over sodium. DCM and THF were dried by a solvent purification system (passed through activated alumina). The vinyldiazoacetate **2**,[4] dimethyl diazomalonate **17b**,[18] methyl phenyldiazoacetate **17c**,[19] and methyl 2-(3-methylisoxazol-5-yl)acetate **20d**[8] were prepared by their respective literature procedures. The synthesis of compounds **9–13, 15**, and **8** is described in the supplementary information. Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. Mass spectral determinations were carried out by LC-MS (ESI), or electron impact ionization (EI). Melting points are uncorrected.

Flash column chromatography was performed on silica gel 60Å (230–400 mesh) using a pentane/diethyl ether mixture as the eluent unless otherwise specified.

4.2. Synthesis of ring expansion/[4 + 3]-cycloaddition product 16

4.2.1. (16)—To a flame dried 25 mL round bottom flask under argon and charged with a stir bar was added **8** (0.0500 g, 0.306 mmol), Rh_2(*R*-DOSP)$_4$ (0.017 g, 0.0092 mmol, 0.03 eq) and 2,2 DMB (2 mL). A reflux condenser was attached to the flask and the solution was heated to reflux. A solution of **2** (0.172 g, 1.23 mmol) in 2,2-DMB (3 mL) was added *via* syringe pump addition over 20 min. The solution was refluxed for another 5 min, then allowed to cool to ambient temperature. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, 5:1-2:1 pentane:diethyl ether) to give the diastereomeric products **16a** (0.038 g, 32% yield) and **16b** (0.036 g, 30% yield) as clear oils.

16a: R_f 0.16 (2:1 pentane:diethyl ether); FTIR (neat): 2930, 1746, 1711, 1640, 1436, 1236, 1193, 1066, 1028, 1006, 970 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 4.5 Hz, 1H), 5.77 (d, *J* = 15.5 Hz, 1H), 5.55 (dq, *J* = 15.5, 6.5 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.55 (m, 1H), 2.67-2.60 (m, 3H), 2.29-2.20 (m, 2H), 1.68 (d, *J* = 6.5 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H), 1.19-1.15 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (C), 167.3 (C), 165.4 (C), 145.5 (CH), 135.9 (CH), 132.9 (CH), 129.9 (C), 127.9 (CH), 126.1 (C), 89.0 (C), 77.6 (C), 52.9 (CH_3), 52.1 (CH_3), 48.5 (CH), 38.6 (CH_2), 37.8 (CH), 31.2 (CH), 27.7 (CH_2), 21.5 (CH_3), 17.6 (CH_3), 14.6 (CH_3), 12.1 (CH_3); LRMS (EI) m/z (relative intensity): 387 (24) $[M]^+$, 328 (100) $[M\text{-}CO_2CH_3]^+$; HRMS (EI) Calcd for $[C_{22}H_{29}NO_5]^+$ 387.2040, Found 387.2041; HPLC analysis: 19% ee (Chiralpak AD-H, 1% *i*-PrOH in hexanes, 0.8 mL/min, λ = 254 nm, t_R = 17.3 min, major; 18.4 min, minor).

16b: R_f 0.31 (2:1 pentane:diethyl ether); FTIR (neat): 2919, 1741, 1710, 1641, 1435, 1234, 1065, 1026, 1003, 970 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 5.0 Hz, 1H), 6.11 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.91 (d, *J* = 15.5 Hz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.57 (m, 1H), 2.72-2.58 (m, 2H), 2.54-2.48 (m, 1H), 2.27-2.21 (m, 2H), 1.78 (d, *J* = 6.5 Hz, 3H), 1.27-1.20 (m, 4H), 0.80 (d, *J* = 6.0 Hz, 3H), 0.78 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (C), 167.3 (C), 165.0 (C), 145.3 (CH), 135.7 (CH), 131.6 (CH), 130.1 (C), 128.5 (CH), 126.0 (C), 87.8 (C), 77.9 (C), 52.3 (CH_3), 52.1 (CH_3), 48.4 (CH), 38.6 (CH_2), 38.4 (CH), 31.2 (CH), 27.5 (CH_2), 18.8 (CH_3), 17.7 (CH_3), 15.0 (CH_3), 11.6 (CH_3); LRMS (ESI) m/z (relative intensity): 388 (100) $[M+H]^+$; HRMS (ESI) Calcd for $[C_{22}H_{30}NO_5]^+$ 388.2118, Found 388.2121; HPLC analysis: 19% ee (Regis *R*,*R*-Whelk, 0.5% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm, t_R = 20.8 min, major; 24.7 min, minor).

4.3 Synthesis of isoxazole 20a

4.3.1 2-(3-Methylisoxazol-5-yl)ethanol—To a flame dried round bottom flask under argon and charged with a stir bar was added methyl 2-(3-methylisoxazol-5-yl)acetate **20d**[8] (0.62 g, 4.0 mmol) and THF (10 mL). The solution was cooled to 0 °C in an ice bath and a solution of LAH (2.0 *M* in THF, 1 mL) was added by syringe. The solution was stirred for 10 min and then slowly quenched with water. The solution was then extracted with ether (3 × 15 mL) and the combined organic extracts dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, diethyl ether as eluent, visualized with $KMnO_4$ stain) to give 2-(3-methylisoxazol-5-yl)ethanol as a clear oil (0.252 g, 50% yield). The characterization data were in agreement with the literature values.[20]

4.3.2 5-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-3-methylisoxazole (20a)—To a flame dried round bottom flask under argon and charged with a stir bar was added 2-(3-methylisoxazol-5-yl)ethanol (0.105 g, 0.83 mmol), TBSCl (0.149 g, 0.99 mmol), DMAP (0.003 g, 0.025 mmol) and DCM (10 mL). Imidazole (0.062 g, 0.91 mmol) was then added

and the solution stirred overnight. The solution was then washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 7:1 pentane:diethyl ether) to give the product as a clear oil (0.107 g, 54% yield). R_f 0.25 (7:1 pentane:diethyl ether); FTIR (neat): 2929, 1607, 1472, 1417, 1255, 1101, 835, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (s, 1H), 3.88 (t, *J* = 6.5 Hz, 2H), 2.92 (t, *J* = 6.5 Hz, 2H), 2.26 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 159.5 (C), 102.5 (CH), 60.6 (CH_2), 30.4 (CH_2), 25.7 (CH_3), 18.1 (C), 11.3 (CH_3), −5.6 (CH_3); LRMS (EI) m/z (relative intensity): 226 (9) $[M]^+$, 184 100 $[M\text{-}^t Bu]^+$; HRMS (EI) Calcd for $[M\text{-}CH_3]^+$ $[C_{11}H_{20}NO_2Si]^+$ 226.1258, Found 226.1249.

4.4. General Procedure for the rhodium catalyzed isoxazole/isothiazole ring expansion reactions

To a flame dried 25 mL round bottom flask under argon and charged with a stir bar was added the isoxazole substrate, $Rh_2(OAc)_4$ and solvent (DCM or 1,2-DCE, 5 mL). A water-cooled condenser was attached to the flask and the solution was heated to reflux. A solution of diazoacetate in solvent (DCM or 1,2-DCE, 5 mL) was then added by syringe pump over 45 min. The solution was refluxed another 15 min and then cooled to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography to give the product.

4.4.1. Ethyl 4,6-dimethyl-2*H*-1,3-oxazine-2-carboxylate (19a)—The reaction was performed with 3,5-dimethylisoxazole **18** (0.146 g, 1.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol) and ethyl diazoacetate **17a** (0.057 g, 0.5 mmol) in 1,2-DCE. Purified by flash chromatography (silica gel, 1:1 pentane:diethyl ether) to give **19a** as a clear oil (0.051 g, 56% yield). R_f 0.13 (1:1 pentane:diethyl ether); FTIR (neat): 2983, 1743, 1619, 1575, 1443, 1385, 1202, 1096, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59 (s, 1H), 5.37 (s, 1H), 4.36-4.26 (m, 2H), 2.04 (s, 3H), 1.98 (s, 3H), 1.34 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 165.8 (C), 162.9 (C), 100.7 (CH), 85.9 (CH), 61.8 (CH_2), 23.7 (CH_3), 19.0 (CH_3), 14.0 (CH_3); LRMS (ESI) m/z (relative intensity): 206 (100) $[M+Na]^+$, 184 (36) $[M+H]^+$; HRMS (ESI) Calcd for $[C_9H_{14}NO_3]^+$ 184.0968, Found 184.0970.

4.4.2. Dimethyl 4,6-dimethyl-2*H*-1,3-oxazine-2,2-dicarboxylate (19b)—The reaction was performed with 3,5-dimethylisoxazole **18** (0.049 g, 0.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol), dimethyldiazomalonate **17b**[18] (0.111 g, 0.70 mmol) and 1,2-DCE. The solution was refluxed for 2 h after the diazo addition was complete. Purified by flash chromatography (silica gel, 1:5 pentane:diethyl ether) to give **19b** as a clear oil (0.053 g, 47% yield). R_f 0.24 (diethyl ether); FTIR (neat): 2950, 1748, 1654, 1574, 1435, 1294, 1259, 1134, 1056, 784, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.39 (s, 1H), 3.86 (s, 6H), 2.10 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 166.2 (C), 162.1 (C), 100.5 (CH), 53.5 (CH_3), 24.1 (CH_3), 19.2 (CH_3), missing C attributed to excessive peak broadening/quadrupolar effect due to N; LRMS (ESI) m/z (relative intensity): 477 (39) $[2M+Na]^+$, 250 (51) $[M+Na]^+$; HRMS (ESI) Calcd for $[C_{10}H_{13}NO_5Na]^+$ 250.0686, Found 250.0680.

4.4.3. Methyl 4,6-dimethyl-2-phenyl-2*H*-1,3-oxazine-2-carboxylate (19c)—The reaction was performed with 3,5-dimethylisoxazole **18** (0.049 g, 0.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol), **17c** (0.132 g, 0.75 mmol) and DCM. Purified by flash chromatography (silica gel, 1.5:1 pentane:diethyl ether) to give **19c** as a white solid (0.109 g, 89% yield). mp = 72–73 °C, R_f 0.19 (1:1 pentane:diethyl ether); FTIR (neat): 2954, 1742, 1659, 1574, 1235, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.40-7.35 (m, 3H), 5.36 (s, 1H), 3.72 (s, 3H), 2.13 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C), 164.7 (C), 162.2 (C), 138.8 (C), 128.6 (CH), 127.9 (CH), 126.2 (CH), 100.7 (CH), 52.7 (CH_3), 23.9 (CH_3), 19.2 (CH_3), missing C attributed to excessive broadening/quadrupolar effect due to N;

LRMS (ESI) m/z (relative intensity): 246 (100) $[M+H]^+$; Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.42; H, 6.17; N, 5.60.

4.4.4. Methyl 6-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-methyl-2-phenyl-2*H*-1,3-oxazine-2-carboxylate(21a)—The reaction was performed with **20a** (0.073 g, 0.30 mmol), $Rh_2(OAc)_4$ (4.0 mg, 0.009 mmol), **17c** (0.064 g, 0.36 mmol) and DCM. Purified by flash chromatography (silica gel, 4:1-3:1 pentane:diethyl ether) to give **21a** as a clear oil (0.098 g, 83% yield). R_f 0.11 (5:1 pentane:diethyl ether); FTIR (neat): 2954, 2928, 2856, 1745, 1658, 1574, 1235, 1098, 1006, 833, 776, 729, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.40-7.35 (m, 3H), 5.43 (s, 1H), 3.87-3.85 (m, 2H), 3.70 (s, 3H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.15 (s, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (C), 164.8 (C), 162.9 (C), 138.8 (C), 128.8 (CH), 128.1 (CH), 126.4 (CH), 101.3 (CH), 78.9 (C), 59.4 (CH_2), 52.8 (CH_3), 37.0 (C), 25.7 (CH_3), 24.1 (CH_3), 18.1 (CH_2), −5.5 (CH_3); LRMS (ESI) m/z (relative intensity): 390 (100) $[M+H]^+$; HRMS (ESI) Calcd for $[C_{21}H_{32}NO_4Si]^+$ 390.2095, Found 390.2091.

4.4.5. Methyl 4-(chloromethyl)-6-methyl-2-phenyl-2*H*-1,3-oxazine-2-carboxylate (21b)—The reaction was performed with 3-chloromethyl-5-methylisoxazole **20b** (0.066 g, 0.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol), **17c** (0.115 g, 0.65 mmol) and DCM. Purified by flash chromatography (silica gel, 5:1 pentane:diethyl ether) to give **21b** as a clear oil (0.130 g, 93% yield). R_f 0.14 (5:1 pentane:diethyl ether); FTIR (neat): 1743, 1655, 1572, 1434, 1369, 1238, 1031, 727, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.41-7.38 (m, 3H), 5.66 (s, 1H), 4.22 (s, 2H), 3.73 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (C), 164.7 (C), 163.0 (C), 138.1 (C), 129.1 (CH), 128.2 (CH), 126.3 (CH), 98.0 (CH), 53.1 (CH_3), 45.5 (CH_2), 19.7 (CH_3), missing C attributed to excessive broadening/quadrupolar effect due to N; LRMS (ESI) m/z (relative intensity): 581 (17) $[2M+Na]^+$, 302 (100) $[M+Na]^+$; HRMS (ESI) Calcd for $[C_{14}H_{14}NO_3ClNa]^+$ 302.0554, Found 302.0557.

4.4.6. Methyl 5-bromo-4,6-dimethyl-2-phenyl-2*H*-1,3-oxazine-2-carboxylate (21c)—The reaction was performed with 4-bromo-3,5-dimethylisoxazole (0.088 g, 0.5 mmol), $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol), **17c** (0.115 g, 0.65 mmol) and DCM. Purified by flash chromatography (silica gel, 7:1 pentane:diethyl ether) to give **21c** as a clear oil (0.155 g, 96% yield). R_f 0.21 (5:1 pentane:diethyl ether); FTIR (neat): 1746, 1638, 1564, 1432, 1376, 1309, 1241, 1137, 1011, 908, 726, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.40-7.38 (m, 3H), 3.72 (s, 3H), 2.34 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (C), 163.1 (C), 160.2 (C), 137.9 (C), 129.0 (CH), 128.8 (C), 128.2 (CH), 126.3 (CH), 97.4 (C), 53.1 (CH_3), 24.4 (CH_3), 19.2 (CH_3); LRMS (ESI) m/z (relative intensity): 324 (10) $[M+H]^+$; HRMS (ESI) Calcd for $[C_{14}H_{15}BrNO_3]^+$ 324.0230, Found 324.0234.

4.4.7. (21d) and (22d)—The reaction was performed with **20d** (0.078 g, 0.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol), **17c** (0.132 g, 0.75 mmol) and DCM. ^1H NMR analysis of the crude reaction mixture in CD_2Cl_2 did not contain **22d**. Purified by flash chromatography (silica gel, 1:1 pentane:diethyl ether) to give a 1:1 mixture of **21d** and **22d** as a sticky white solid (0.102 g, 67% yield). R_f 0.17 (1:1 pentane:diethyl ether); ^1H NMR (500 MHz, $CDCl_3$) δ 7.73-7.71 (m, 2H), 7.57-7.56 (m, 2H), 7.40-7.39 (m, 6H), 6.45 (s, 1H), 6.00 (s, 1H), 5.45 (s, 1H), 5.19 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 3.33 (s, 2H), 2.24 (s, 3H), 2.03 (s, 3H); LRMS (ESI) m/z (relative intensity): 629 (85) $[2M+Na]^+$, 326 (100) $[M+Na]^+$; HRMS (EI) Calcd for $[C_{16}H_{17}NO_5]^+$ 303.1101, Found 303.1111.

4.4.8. Methyl 2-phenyl-2*H*-benzo[*e*][1,3]oxazine-2-carboxylate (24)—The reaction was performed with freshly purified 1,2-benzisoxazole **23** (0.065 g, 0.55 mmol, purified by passing through a silica gel pipet column eluted with 5:1 pentane:diethyl ether), $Rh_2(OAc)_4$ (7

mg, 0.016 mmol), **17c** (0.044 g, 0.25 mmol) and DCM. Purified by flash chromatography (silica gel, 2:1-1:1 pentane:diethyl ether) to give **24** as a clear oil (0.048 g, 72% yield). R_f 0.23 (1:1 pentane:diethyl ether); FTIR (neat): 2950, 1745, 1633, 1608, 1229, 1050, 1035, 1003, 759, 727, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.76 (d, *J* = 7.0 Hz, 2H), 7.42-7.32 (m, 4H), 7.22 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.98 (*appt* t, *J* = 7.0 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C), 157.5 (CH), 153.2 (C), 138.6 (C), 134.5 (CH), 128.8 (CH), 128.1 (CH), 127.4 (CH), 126.4 (CH), 122.0 (CH), 116.7 (C), 116.5 (CH), 91.7 (C), 53.1 (CH_3); LRMS (ESI) m/z (relative intensity): 268 (27) $[M+H]^+$; HRMS (ESI) Calcd for $[C_{16}H_{14}NO_3]^+$ 268.0968, Found 268.0969.

4.4.9. Aziridine 25—The reaction was performed with freshly purified 1,2-benzisoxazole **23** (0.065 g, 0.55 mmol, purified by passing through a silica gel pipet column eluted with 5:1 pentane:diethyl ether), $Rh_2(OAc)_4$ (7 mg, 0.016 mmol), **17c** (0.291 g, 1.65 mmol) and DCM. Purified by flash chromatography (silica gel, 3:1–2:1 pentane:diethyl ether) to give **25** as a white solid (0.215 g, 94% yield). mp 147–149 °C; R_f 0.36 (1:1 pentane:diethyl ether); FTIR (neat): 2950, 1742, 1491, 1281, 1208, 1128, 1074, 1045, 1031, 986, 759, 727, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) . 7.84 (d, *J* = 7.0 Hz, 2H), 7.80 (d, *J* = 7.0 Hz, 2H), 7.44-7.36 (m, 3H), 7.29-7.15 (m, 5H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.95-6.92 (m, 1H), 3.83 (s, 3H), 3.60 (s, 3H), 3.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 167.4 (C), 149.5 (C), 137.5 (C), 137.0 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 127.0 (CH), 122.8 (CH), 120.3 (C), 118.5 (CH), 89.5 (C), 53.0 (CH_3), 52.7 (C), 52.3 (CH_3), 44.4 (CH), 2 missing CH resonances attributed to overlapping signals; LRMS (ESI) m/z (relative intensity): 853 (100) $[2M+Na]^+$, 438 (36) $[M+Na]^+$; Anal. Calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37. Found: C, 71.92; H, 5.09; N, 3.33.

4.4.10. Methyl 2-(2-formylphenylimino)-2-phenylacetate (27)—The reaction was performed with anthranil **26** (0.179 g, 1.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol), **17c** (0.085 g, 0.5 mmol) and 1,2-DCE. Purified by flash chromatography (silica gel, 5:1 pentane:diethyl ether) to give **27** (0.089 mg, 67% yield) and **28** (0.034 g, 16% yield) as yellow oils. **27**: R_f 0.30 (2:1 pentane:diethyl ether); FTIR (neat): 1733, 1690, 1624, 1592, 1450, 1302, 1273, 1226, 1192, 1174, 1155, 1009, 764, 689, 669 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 10.20 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.60-7.49 (m, 4H), 7.26 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 3.58 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 190.3 (CH), 164.7 (C), 161.7 (C), 152.7 (C), 135.1 (CH), 133.5 (C), 132.8 (CH), 129.2 (CH), 128.6 (CH), 128.3 (CH), 127.0 (C), 125.5 (CH), 119.4 (CH), 52.4 (CH_3); LRMS (ESI) m/z (relative intensity): 557 (52) $[2M+Na]^+$, 290 (100) $[M+Na]^+$, 268 (68) $[M+H]^+$; HRMS (EI) Calcd for $[C_{16}H_{13}NO_3]^+$ 267.0890, Found 267.0903.

4.4.11. (*E*)-Methyl3-(2-(2-methoxy-2-oxo-1-phenylethylideneamino)phenyl)-2-phenyloxirane-2-carboxylate (28)—The reaction was performed with anthranil **26** (0.060 g, 0.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol), **17c** (0.255 g, 1.5 mmol) and 1,2-DCE. Purified by flash chromatography (silica gel, 5:1 pentane:diethyl ether) to give **28** as a yellow oil (0.201 g, 97% yield). R_f 0.24 (2:1 pentane:diethyl ether); FTIR (neat): 1734, 1449, 1434, 1298, 1234, 1197, 1171, 1009, 763, 739, 691 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.87 (d, *J* = 7.0 Hz, 2H), 7.57-7.54 (m, 1H), 7.49-7.45 (m, 5H), 7.31-7.17 (m, 5H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.33 (s, 1H), 3.64 (s, 3H), 3.48 (s, 3H);); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 167.6 (C), 165.3 (C), 160.6 (C), 148.9 (C), 135.8 (C), 133.9 (C), 132.5 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.52 (CH), 128.48 (CH), 127.5 (CH), 126.5 (CH), 126.2 (C), 125.3 (CH), 117.4 (CH), 66.8 (C), 63.1 (CH), 52.4 (CH_3), 52.3 (CH_3); LRMS (ESI) m/z (relative intensity): 438 (100) $[M+Na]^+$, 416 (41) $[M+H]^+$; HRMS (EI) Calcd for $[C_{25}H_{21}NO_5]^+$ 415.1414, Found 415.1416.

4.4.12. Methyl 2-(2-benzoyl-4-chlorophenylimino)-2-phenylacetate (30)—The reaction was performed with 5-chloro-3-phenylanthranil **29** (0.115 g, 0.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol), **17c** (0.106 g, 0.6 mmol) and DCM. Purified by flash chromatography (silica gel, 5:1 pentane:diethyl ether) to give **30** as a sticky yellow oil (0.185 g, 98% yield). R_f 0.24 (5:1 pentane:diethyl ether); FTIR (neat): 1734, 1664, 1449, 1283, 1226, 1195, 1173, 1009, 688 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.81 (d, *J* = 7.0 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.05-6.95 (m, 5H), 6.92-6.89 (m, 2H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 195.1 (C), 164.7 (C), 160.4 (C), 147.2 (C), 137.7 (C), 133.6 (C), 133.3 (CH), 132.9 (C), 132.5 (CH), 131.8 (CH), 130.7 (C), 130.1 (CH), 129.9 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 120.8 (CH), 52.5 (CH_3); LRMS (ESI) m/z (relative intensity): 777 (100) $[2M+Na]^+$, 400 (100) $[M+Na]^+$, 378 (18) $[M+H]^+$; HRMS (EI) Calcd for $[C_{22}H_{16}NO_3Cl]^+$ 377.0813, Found 377.0826.

4.4.13. Methyl 4-chloro-2-phenyl-2*H*-benzo[*e*][1,3]thiazine-2-carboxylate (32)—The reaction was performed with 3-chloro-1,2-benzisothiazole **31** (0.085 g, 0.5 mmol), $Rh_2(OAc)_4$ (6.6 mg, 0.015 mmol), **17c** (0.115 g, 0.65 mmol) and DCM (5 mL). Purified by flash chromatography (silica gel, 3:1 pentane:diethyl ether) to give **32** as a clear oil (0.140 mg, 88% yield). R_f 0.25 (2:1 pentane:diethyl ether); FTIR (neat): 2966, 1736, 1446, 1434, 1234, 1007, 819, 764, 733, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.55-7.54 (m, 2H), 7.51-7.46 (m, 2H), 7.34 (m, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C), 137.8 (CH), 136.8 (C), 133.7 (CH), 133.2 (C), 132.3 (CH), 130.3 (CH), 129.2 (CH), 128.2 (CH), 127.0 (CH), 120.5 (C), 117.0 (C), 82.3 (C), 54.3 (CH_3); LRMS (EI) m/z (relative intensity): 317 (5) $[M]^+$, 121 (100); HRMS (EI) Calcd for $[C_{16}H_{12}ClNO_2S]^+$ 317.0272, Found 317.0265.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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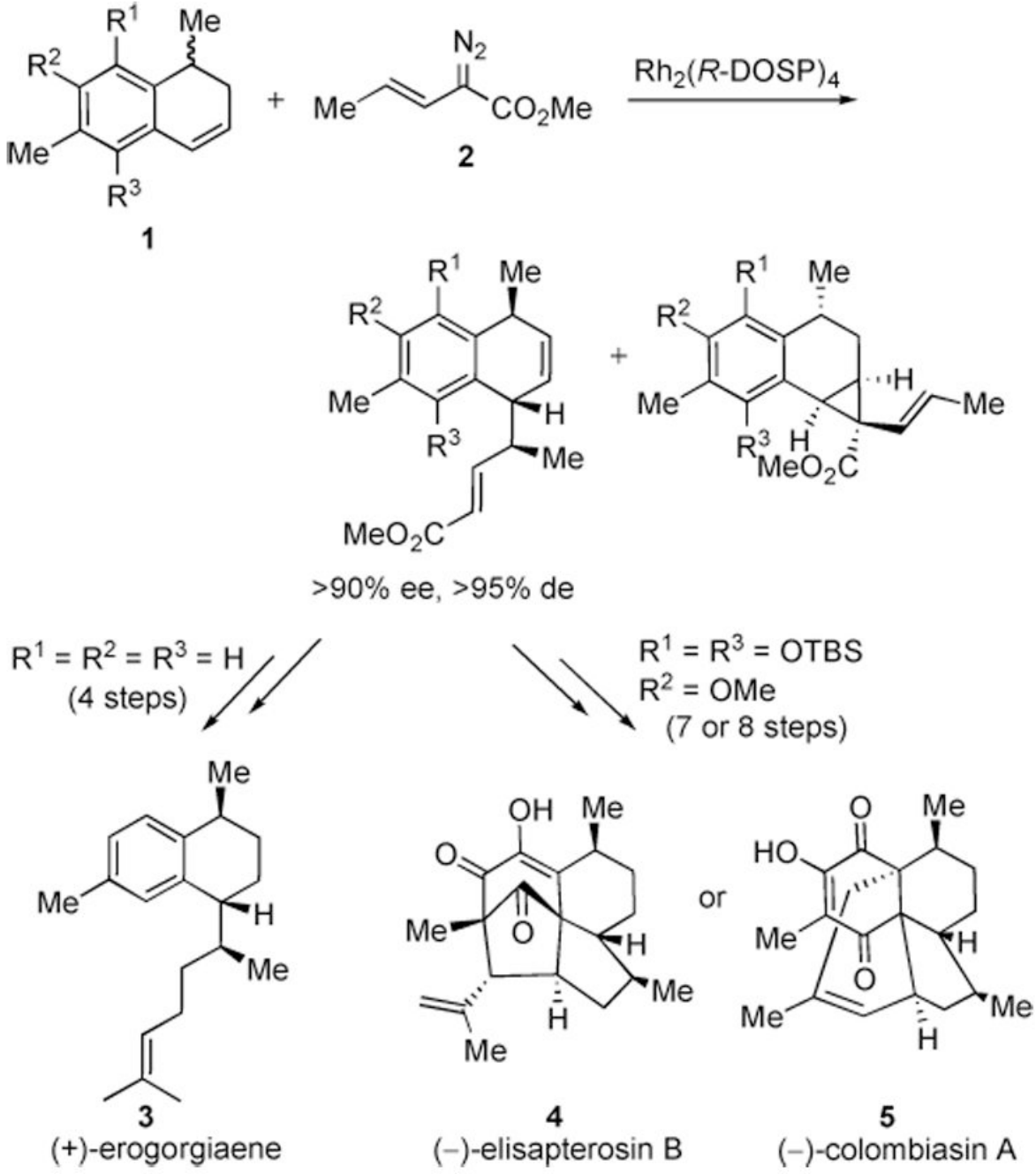
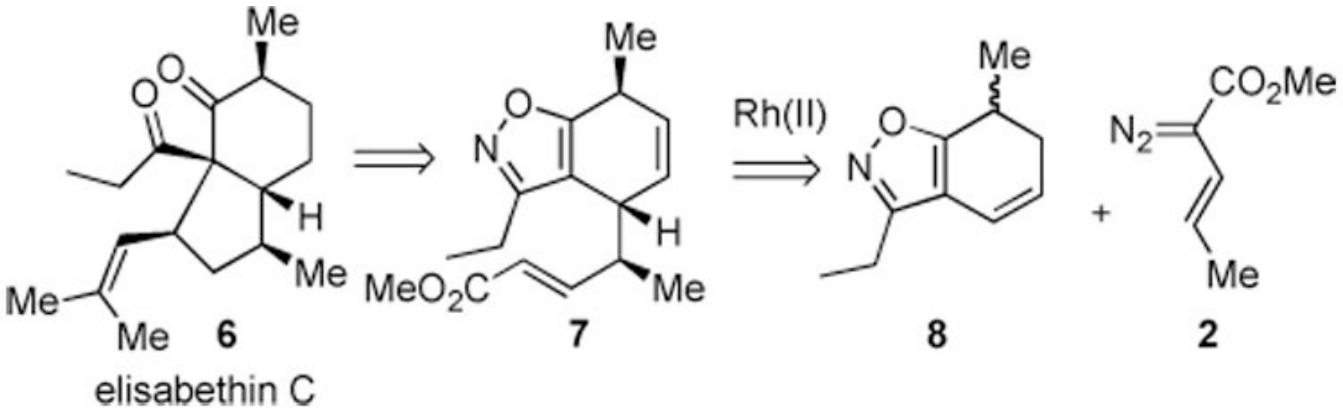
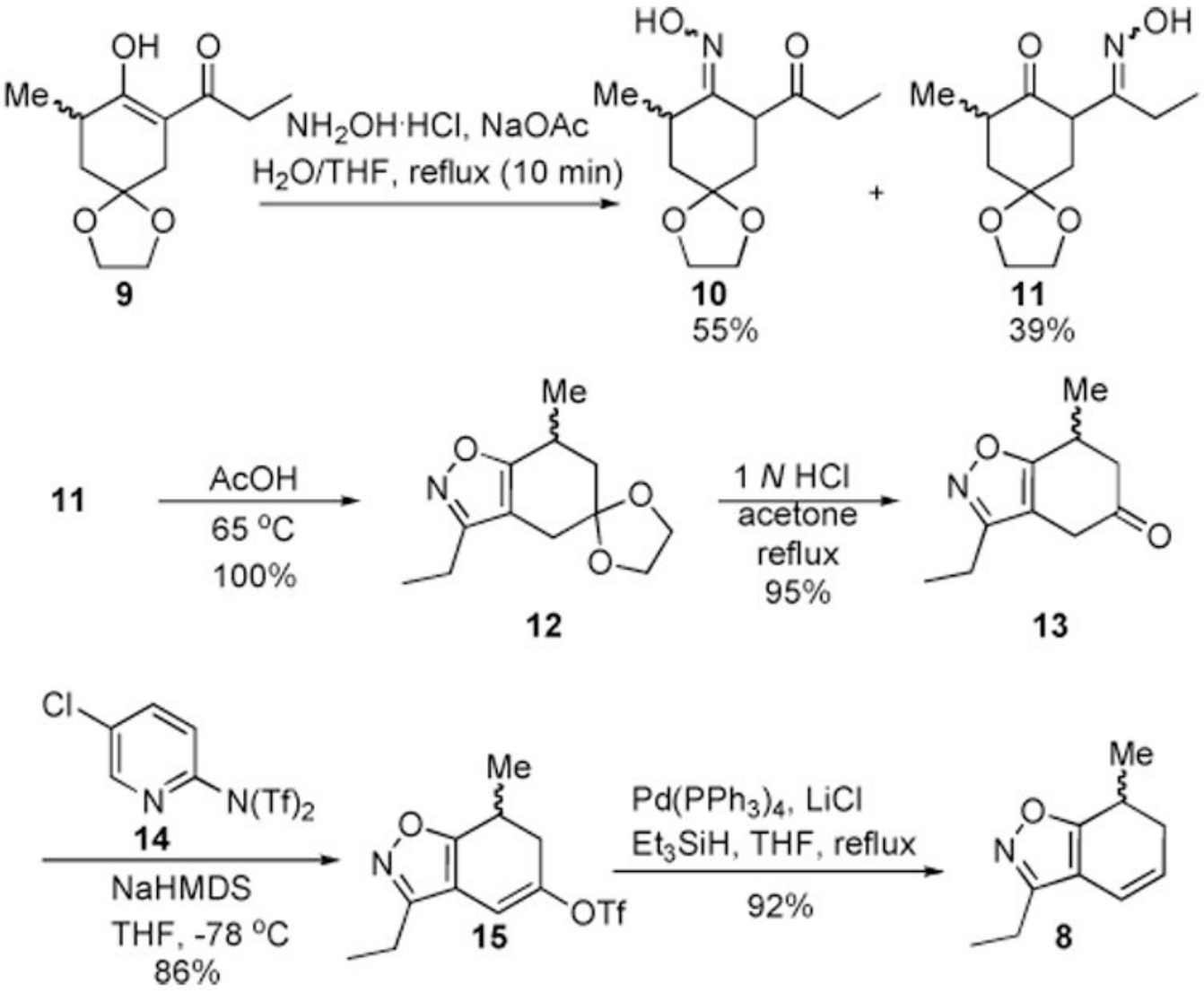


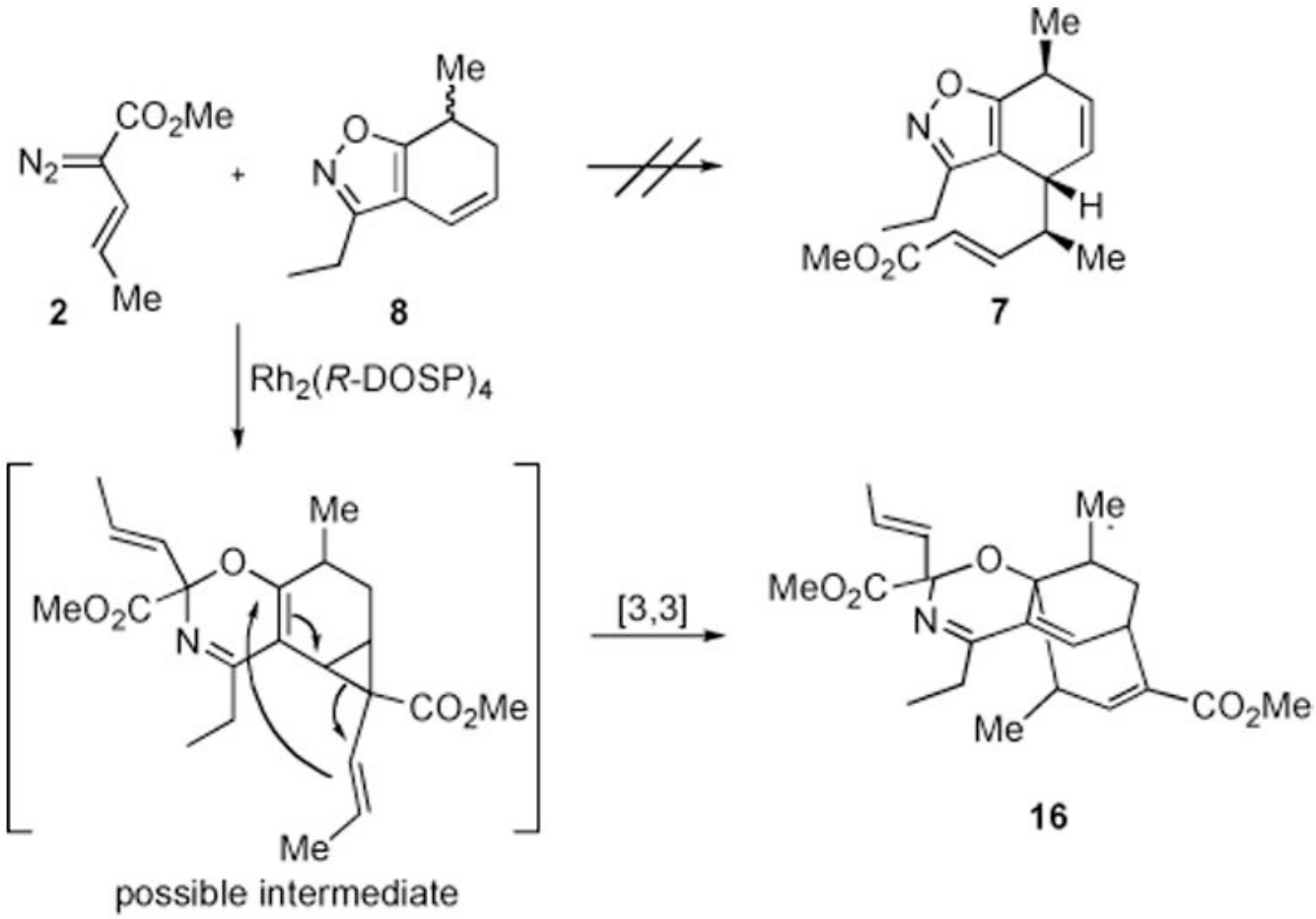
Scheme 1.
Synthesis of Marine Natural Products



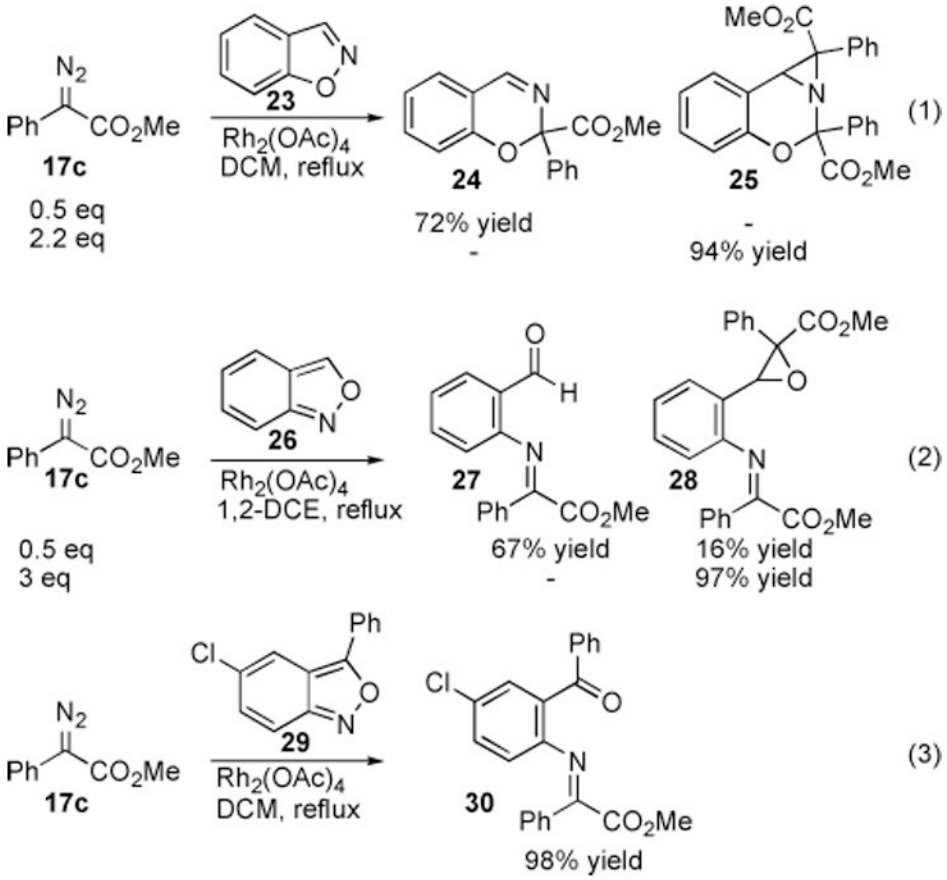
Scheme 2.
Retrosynthesis of Elisabethin C



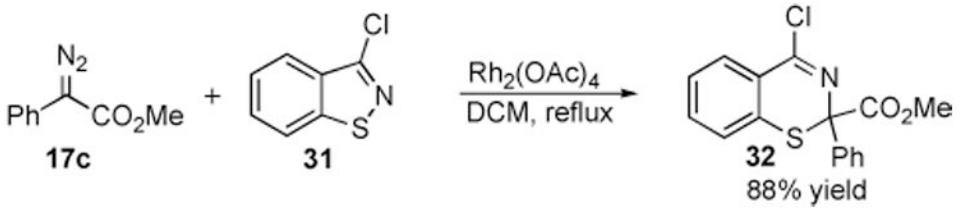
Scheme 3.
Synthesis of Dihydrobenzoisoxazole **8**



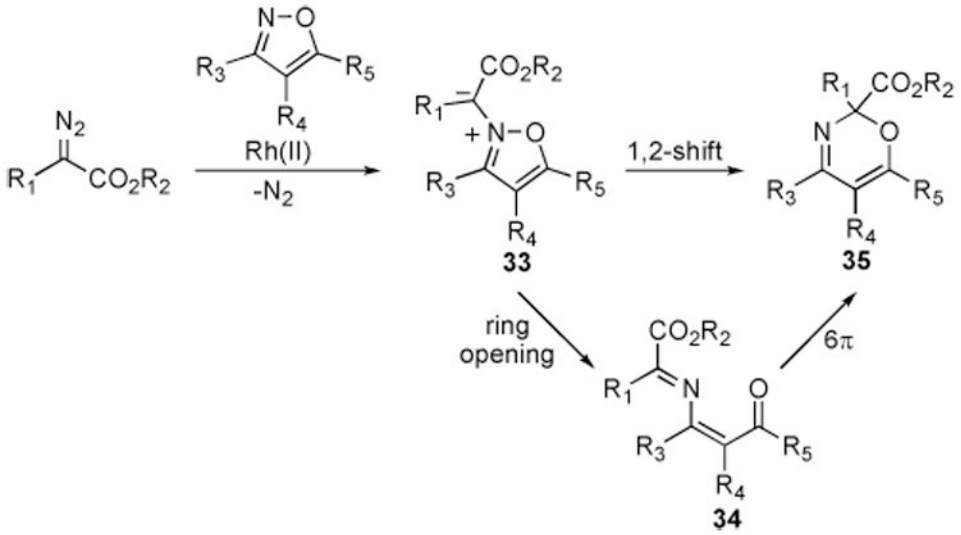
Scheme 4.
Reaction of **8** with a Vinylcarbenoid



Scheme 5.
Reaction of Diazoacetate **17c** with Benzisoxazoles



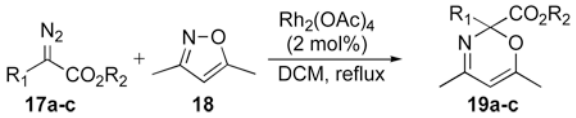
Scheme 6.
Ring Expansion of an Isothiazole



Scheme 7.
Possible Mechanistic Pathways for Isoxazole Ring Expansion

Table 1

Reaction of Rhodium Carbenoids with 3,5-Dimethylisoxazole

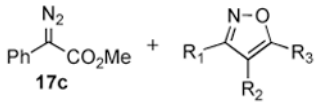


entry	R_1	R_2	19	yield, %[a]
1	H	Et	**19a**	56
2	CO_2Me	Me	**19b**	47
3	Ph	Me	**19c**	88

[a]Reported yields are of isolated products.

Table 2

Reaction of diazoacetate **17c** with isoxazoles



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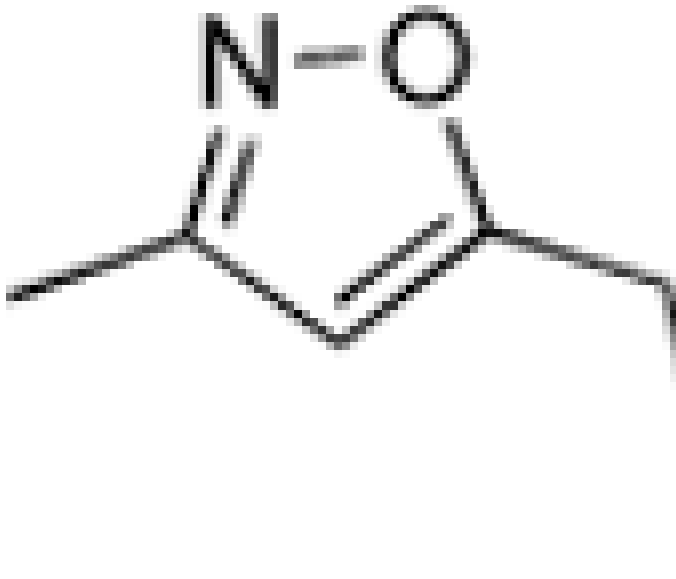
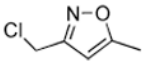
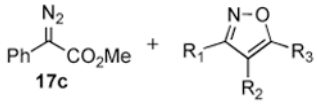
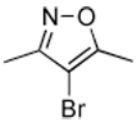
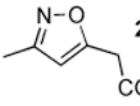
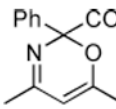
1	 **20a**	
2	 **20b**	



entry	isoxazole	product
3	 **20c**	
4	 **20d**	

[a] Reported yields are of isolated products.

[b] During attempted purification, product formed a 1:1 inseparable mixture with its tautomer **22d.**