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Nickel-Catalyzed Cyclizations of Enoates and Chiral Allenes: An Approach to Domoic Acid

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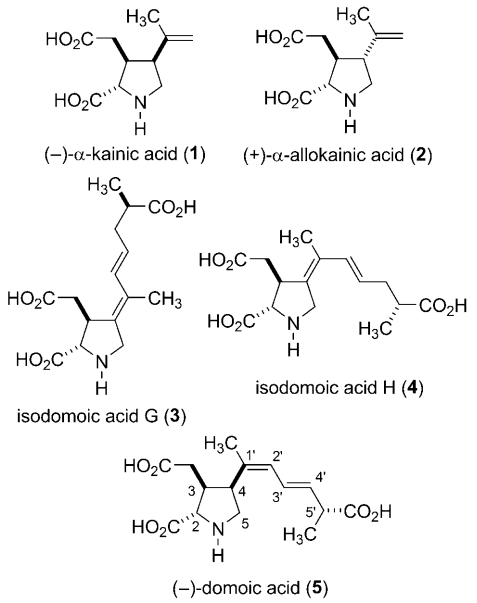
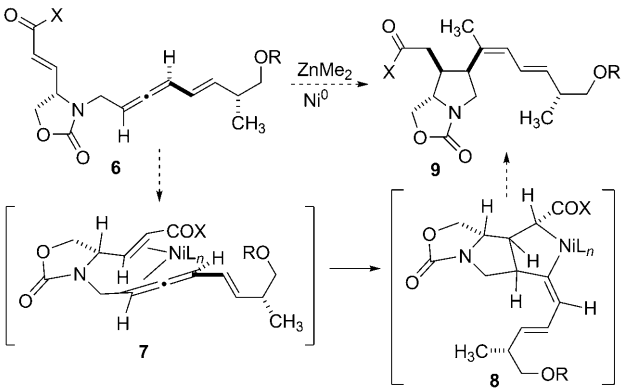
The kainoid family of marine natural products has attracted considerable interest due to the potent pharmacological properties of compounds in this class.[1] By serving as conformationally restricted analogues of glutamate, this group of natural products displays potent neuroexcitatory activity, and the more complex members of the domoic acid type have been responsible for outbreaks of poisoning from mussel toxins.[2] The kainic acid and domoic acid families of natural products include a diverse range of structures that possess highly functionalized pyrrolidine di- or triacid motifs (**1**–**5** shown here).[3] Kainic and allokainic acids possess a simple C4 propenyl substituent, whereas domoic acid and its isomers possess more complex C4 functionality. Our interest in the synthesis of members of this class of compounds has led to the development of a number of nickel-catalyzed processes, including the alkylative cyclization of enoate–alkyne and enoate–allene substrates. These processes have served as key steps in the total syntheses of kainic acid (**1**), allokainic acid (**2**), and isodomoic acids G (**3**) and H (**4**).[4–6] We envisioned that the development of a related cyclization method involving cyclization of an enoate tethered with a chiral allene would allow synthesis of the remaining members of the domoic acid class, including domoic acid (**5**), that do not possess the C4 exocyclic functionality seen in isodomoic acids G and H. Herein, we describe an initial investigation of this strategy, and the synthesis of a model substructure of domoic acid.



Our first-generation strategy for the synthesis of domoic acid (**5**) features an ambitious dimethyl zinc-mediated cyclization of enoate–allene **6**.[7] As depicted (Scheme 1), we anticipated that the allene chirality of **6** would ultimately establish stereochemistry in the generation of the C3 and C4 stereocenters and the C1′-trisubstituted alkene of **9** during the cyclization.[8] Our mechanistic hypothesis involves formation of a Ni^0–π complex **7** with an eclipsed orientation of the reactive π systems, followed by the formation of metallacycle **8**, in which all of the key stereochemical features are established.[9] The prediction that the proximal π system of the allene will undergo coupling draws from our earlier observations made in the synthesis of kainic acid,[4b] as well as related five-membered aldehyde–allene alkylative cyclization processes.[7d]



Scheme 1. First-generation strategy.

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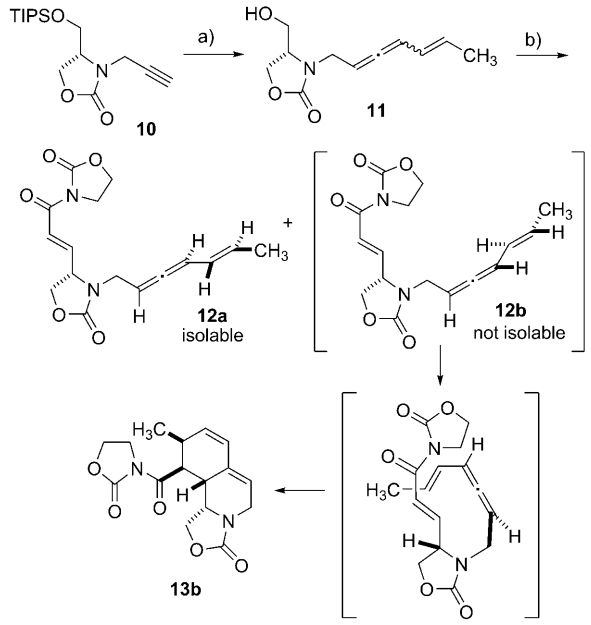
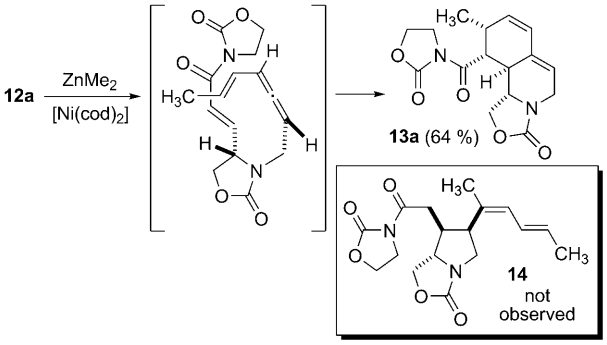


Scheme 2. Examination of vinyl allene cyclizations. a) i. **10**, *n*BuLi, then crotonaldehyde, THF, −50 °C, 65 %, ii. Bu_3SnH, AIBN, 90 °C, then MsCl, Et_3N, CH_2Cl_2, then $(nBu)_4NF$, THF, 45 %; b) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 to −20 °C, then [(2-oxooxazolidin-3-yl)methyl]triphenylphosphonium bromide, DMAP, −20 °C to RT, 14 % of **12a**, 31 % of **13b**. AIBN = azobisisobutyronitrile; MsCl = methanesulfonyl chloride; DMAP = 4-dimethylaminopyridine.

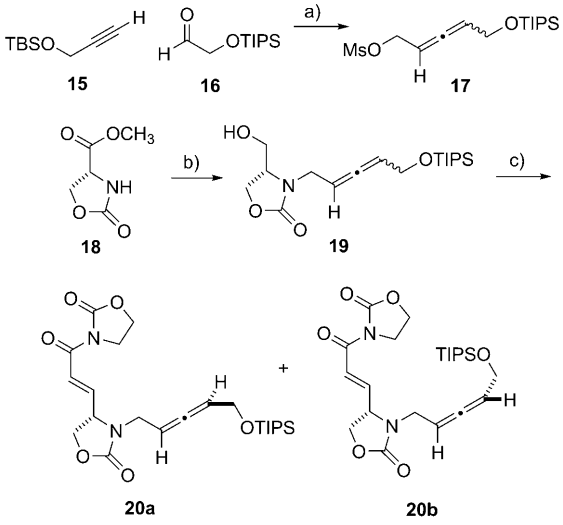


Scheme 3. Attempted vinyl allene alkylative cyclization.

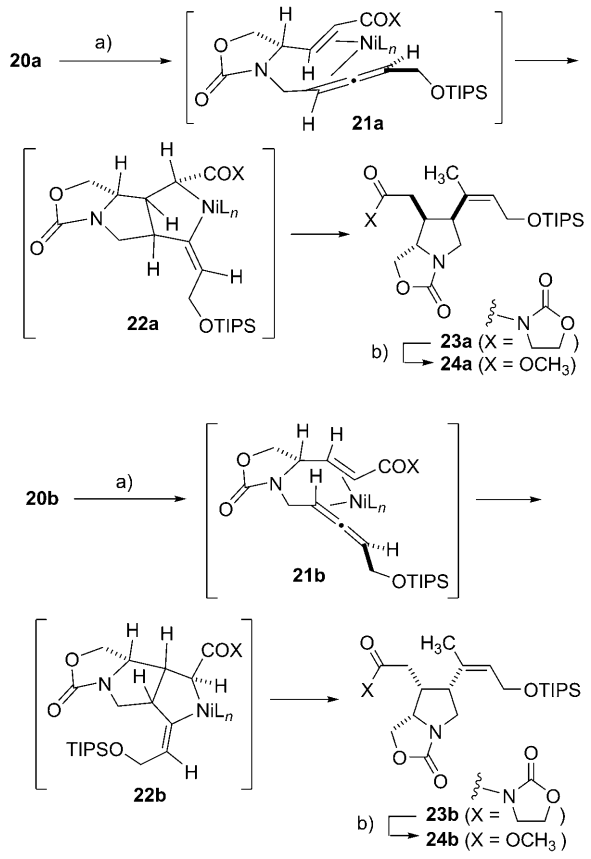
For our initial examination of this approach, the requisite substrate **12** was first prepared (for ease of synthesis) as a mixture of allene epimers beginning from alkyne **10** (Scheme 2). Our earlier studies had illustrated that unsaturated acyl oxazolidinones were the most effective enoate derivatives in nickel cyclization processes.[4] Upon conversion of alcohol **11** to enoate **12**, one of the diastereomers of **12** was found to be unstable, based on facility of an undesired Diels–Alder cycloaddition to afford product **13b** along with a single diastereomer of the desired enoate **12a**. The facility of this cycloaddition is notable given the comparatively harsh conditions required for other types of vinyl allene Diels–Alder reactions.[10] Based on the stereochemical outcome of the generation of product **13b**, allene **12b** can be assumed to be the unstable allene diastereomer that undergoes rapid cycloaddition to **13b**, and allene **12a** is therefore the diastereomer that is isolable.

As structure **12a** is the diastereomer anticipated to be required for the nickel-catalyzed cyclization, its participation in an alkylative cyclization reaction was examined (Scheme 3). However, we were unable to access the desired product **14**. Instead, Diels–Alder cycloaddition predominated to afford structure **13a**, providing further proof of the structure of diastereomer **12a**. It is unclear if the cycloaddition is catalyzed by $[Ni(cod)_2]$ (cod = cyclooctadiene) or $ZnMe_2$, and due to the limited material available, this question was not explored.[11,12] Instead, we opted to redesign the strategy by removing the C3′–C4′ unsaturation, thus removing the complexity of the competing Diels–Alder cycloaddition.

To pursue this second-generation strategy, racemic allenyl mesylate **17** was prepared by a straightforward route from alkyne **15** and aldehyde **16** (Scheme 4). *N*-Alkylation of **18** with mesylate **17** followed by ester reduction afforded **19** as a mixture of allene epimers. Oxidation state adjustment and olefination of **19** provided diastereomers **20a** and **20b**, which were separated by preparative HPLC. This route was attractive in that both diastereomers of **20** were made available for investigation, and the stereochemistry of **20a** was later confirmed by independent asymmetric synthesis (vide infra).



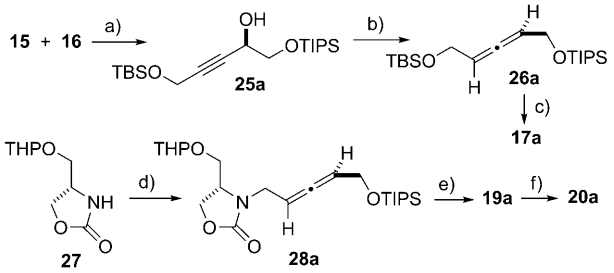
Scheme 4. Preparation of cyclization substrates. a) i. **15**, *n*BuLi, THF, −78 °C, then **16**, 65 %, ii. PPh_3, DEAD, *o*-nitrobenzene sulfonyl hydrazine, THF, −15 °C to RT, 61 %, iii. PPTS, EtOH, 55 °C, 85 %, iv. MsCl, Et_3N, CH_2Cl_2, 0 °C, 98 %; b) i. KHMDS, **17**, THF, 0 °C, 41 %, ii. $NaBH_4$, EtOH, 0 °C, 80 %; c) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 to −20 °C, then [(2-oxooxazolidin-3-yl)methyl]triphenylphosphonium bromide, DMAP, −20 °C to RT, 69 % combined of **20a** and **20b** (1:1, separated by HPLC). DEAD = diethyl azodicarboxylate; PPTS = pyridinium *p*-toluenesulfonate; MsCl = methanesulfonyl chloride; KHMDS = potassium hexamethyldisilazide; DMAP = 4-dimethylaminopyridine.



Scheme 5. Alkylative cyclization of an enoate/chiral allene. a) $ZnCl_2$, MeLi, Ti(O-*i*Pr)$_4$, [Ni(cod)$_2$] (20 mol%), −20°C to RT, 77% (in the case of **23a**), 24% (in the case of **23b**); b) MeOMgBr, toluene/THF, 0°C to RT, 75% (in the case of **24a**), 79% (in the case of **24b**).

With allene epimers **20a** and **20b** both in hand, nickel-catalyzed, dimethyl zinc promoted cyclization was investigated (Scheme 5). Gratifyingly, as anticipated from our strategic plan, cyclization of **20a** cleanly afforded desired compound **23a**, whereas cyclization of **20b** under identical conditions afforded diastereomer **23b** in a less-efficient and lower yielding cyclization. The π complex **21a**, followed by cyclization to metallacycle **22a**, likely explains the stereochemical outcome of this key cyclization process in the formation of **23a**.[9] Alternatively, by utilizing the opposite allene chirality, modified orientation of substrate **20b** in π complex **21b**, followed by cyclization to metallacycle **22b**, provides diastereomer **23b**. This outcome illustrates that the allene chirality is essential in establishing the desired C3 and C4 stereochemical arrangement. Oxazolidinones **23a** and **23b** were cleanly converted to methyl esters **24a** and **24b** in straightforward fashion.

Lastly, an improved route to compound **24a** involving asymmetric synthesis of the requisite allene fragment and an improved entry to a pyrrolidine precursor was developed (Scheme 6). Enantioselective addition of alkyne **15** to aldehyde **16** following the method of Carreira provided alcohol **25a** in 94% *ee*,[13] and subjecting this structure to the allylic diazene method of Myers provided allene **26a** in 92% *ee*.[14]



Scheme 6. Enantioselective preparation of a cyclization precursor. a) zinc trifluoromethane sulfonate, (1*R*, 2*S*)-(−)-*N*-methylephedrine, **15**, then **16**, toluene, RT, 58% (94% *ee*); b) PPh_3, DEAD, *o*-nitrobenzene sulfonyl hydrazine, THF, −15°C to RT, 61% (92% *ee*); c) i. PPTS, EtOH, 55°C, 85%, ii. MsCl, Et_3N, CH_2Cl_2, 0°C, 98%; d) **17a**, **27**, benzyltriethylammonium bromide, 50% NaOH, CH_2Cl_2, 50%, e) PPTS, EtOH, 55°C, 76%. f) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 to −20°C, then [(2-oxooxazolidin-3-yl)methyl]triphenylphosphonium bromide, DMAP, −20°C to RT, 74%. DEAD = diethyl azodicarboxylate; PPTS = pyridinium *p*-toluenesulfonate; MsCl = methanesulfonyl chloride; DMAP = 4-dimethylaminopyridine.

Conversion to mesylate **17a** and *N*-alkylation of **27** provided access to diastereomerically pure **28a**. Conversion of **28a** to **19a** and then **20a** completed the stereoselective approach to **24a** and confirmed the structures of diastereomers **20a** and **20b**. In this route, precursor **27** was utilized rather than *N*-alkylation of **18** in order to avoid a problematic epimerization that had been observed in our parallel efforts to synthesize isodomoic acids G and H.[4d] This improved entry to compound **24a** avoids the tedious separation of **20a** and **20b** and provides a selective entry to the substructure that directly corresponds to that seen in domoic acid and a range of naturally occurring isodomic acid structures.

In summary, the first examples of enoate/chiral allene alkylative cyclizations have been demonstrated. The process is effective in the synthesis of functionalized pyrrolidine derivatives that possess stereodefined alkenyl substituents. An advanced intermediate towards the synthesis of domoic acid was prepared using this method. The efficient synthesis of structure **24a** may be useful in future synthetic approaches to domoic acid and several naturally occurring isodomoic acids. A notable feature of this approach is that the C3−C4 bond, the C3 and C4 stereogenic centers, and the C1′−C2′-trisubstututed alkene are introduced efficiently and with high selectivity in this new catalytic process.

Experimental Section

Preparation of compound 23a: , MeLi (0.66 mL, 1.0 mmol, 1.5 M in diethyl ether) was added dropwise to a solution of anhydrous $ZnCl_2$ (68 mg, 0.5 mmol) in THF (0.5 mL) at 0°C. After stirring for 10 min at 0°C, the mixture was transferred by cannula to a flask containing a solution of [Ni(cod)$_2$] (12 mg, 0.04 mmol) in THF (5 mL) at 0°C. The mixture was cooled to −20°C, then a solution of **20a** (100 mg, 0.2 mmol) and titanium isopropoxide (60 mg, 60 μL, 0.2 mmol) in THF (8 mL) was added dropwise. The mixture was slowly warmed to RT, stirred for 2 h, quenched with sat. NH_4Cl, and extracted with ethyl acetate. The combined extracts were washed with brine and dried over $MgSO_4$. After fil-

tration, the solvent was removed under vacuum, and the crude product was purified by flash column chromatography (hexane/ethyl acetate, 2:1 to 1:2) to yield 78 mg (77%, 94:6 *dr*) of **23a** as a thick oil.

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