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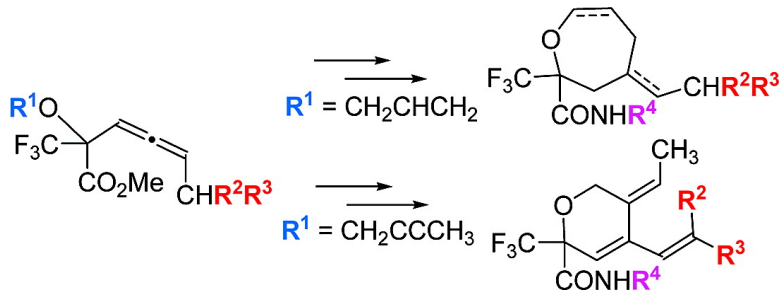

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Diverging Rh(I)-Catalyzed Carbocylization Strategy to Prepare a Library of Unique Cyclic Ethers

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A library of 90 carboxamide-containing oxepines and pyrans was synthesized. A dual-branching strategy was used where a common intermediate, an allenyl-hydroxy ester, was either allylated or propargylated then subjected to rhodium(I)-catalyzed carbocyclization reaction conditions to afford an oxepine- or triene-containing pyran, respectively. The oxepines were selectively reduced to afford two functionally unique scaffolds using complementary hydrogenation conditions. Diversification of the oxepines and pyrans involved conversion of the methyl carboxylate group to a carboxamide via either a microwave-assisted amidation using polymer-bound carbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) or a NaCN-catalyzed aminolysis. The scope of a rarely used carbonyl-yne reaction was expanded to the preparation of 10 new allenyl-hydroxy esters using microwave irradiation. Finally, a cell-based diversity analysis using BCUT (Burden (B) CAS (C) Pearlman at the University of Texas (UT)) metrics calculations and two-dimensional fingerprint similarity approaches shows that when compared to the 100 000 Pittsburgh Molecular Library Screening Center (PMLSC) compound database and PubChem the new compound library occupies a unique chemical space.

Introduction

Strategies for achieving diversity-oriented synthesis (DOS)[1–4] have been divided into four main categories: (1) appendage diversity; (2) stereochemical diversity; (3) skeletal diversity; and (4) building block diversity.[5] To date, skeletal diversity[6–10] has been the most difficult to achieve, the major challenge being identification of differentiating processes that meet the challenges imposed by library synthesis. Identification of enabling technologies for the preparation of skeletally unique compounds via differentiating reactions will provide a mechanism for permeating the void in chemical space.[11] In conjunction with our efforts to develop novel allenyl cyclocarbonylation and cycloisomerization processes, we embarked on investigations of new DOS strategies: mainly, converting a common precursor to structurally unique compounds via reagent controlled skeletal reorganization processes.

Previously, we have demonstrated that a single allene-yne **1**, possessing an amino-acid tether (X = NBz or NBoc), can be converted to methylenecyclopenta[*c*]pyrrol-5(1*H*)-one **2**, cyclopenta[*c*]pyridin-6(5*H*)-one **3**, or vinyl piperidinyl **4**, and cyclobutenyl[*c*]pyridine **5** containing compounds by varying only the transition-metal catalyst or the reaction condition (Figure 1).[12] In addition, the corresponding *ene*-allene **1** is transformed to the tetrahydroazepinyl-containing substructure **6**. An advantage to this DOS strategy is the synthetic efficiency of obtaining multiple skeletons from one compound. The efficiency of this diverging approach to skeletal diversity has been demonstrated by the work of the University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD) in preparation of multiple chemical libraries[13] possessing compounds with interesting biological activity.[14] Efforts are continuing in our laboratory, to explore the scope and limitations of this DOS approach as a means of gaining efficient access to natural productlike compounds.[15]

Herein, we describe our efforts to design and synthesize a new common intermediate **1** (X = O) possessing an α-alkoxy ester. In addition, we report the use of **1** in the preparation of a library of unique oxepine- and pyran-containing compounds, a common moiety in a number of biologically relevant compounds, a few of which are shown in Figure 2.[16] These structures range from the very complex polycycles (bruceantin, brevetoxin, and artemisinin) to the monocycles (zoapatanol and lobatrienol[17]).

There are a number of strategies directed toward the synthesis of oxepines, and they have been reviewed recently.[16] Among them, the enol ether oxepine is of great

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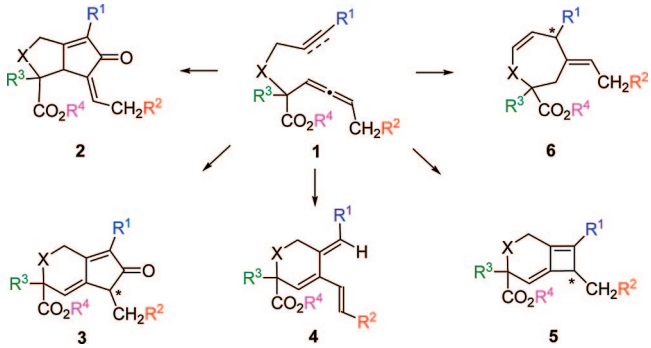


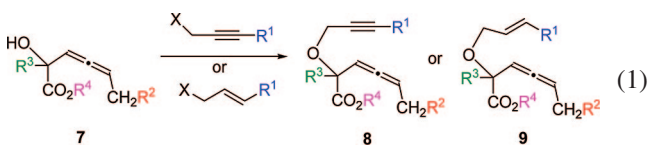
Figure 1. Diverging approach to skeletal diversity.

interest since it can be further functionalized (e.g., via epoxidation and nucleophilic attack) to provide more complex structures.[18] One way of synthesizing these compounds is to use transition-metal (e.g., ruthenium, rhodium, molybdenum, tungsten) mediated cycloisomerization of alkynols.[19] Another approach is to use palladium(0)-mediated cyclization of an oxygen nucleophile with a bromoallene.[20] In addition, another useful method is the intramolecular addition of a hydroxyl group onto an acetal, followed by a base-mediated elimination.[18a,21] The Brummond group developed a Rh(I)-catalyzed allenic carbocyclization reaction to generate enol ether oxepines, and it is that method that is described in this paper.

Results and Discussion

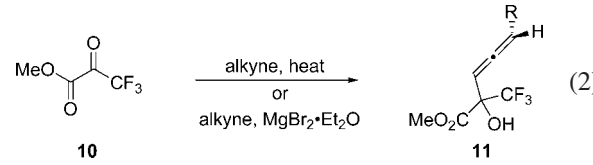
Designing a new and versatile common intermediate that could be used in the preparation of libraries of structurally unique compounds, which are of potential biological relevance, was our initial challenge. In previous studies, we had established the scope and limitations of the amino-ester derived allene-yne common precursor and thus used this information in our design. In order to maximize the diversity potential of the common intermediate, the following structural requirements were considered: the ability to append either a *trans*-alkene or an internal alkyne subunit to the allene; at least one hydrogen atom on the carbon possessing R^2; and the incorporation of at least one versatile functional group for back-end diversifications.

A survey of the literature revealed the allenyl hydroxy ester **7** (R^2 = propyl, R^3 = CF_3, R^4 = CH_3) was available via a one-step procedure from 1-hexyne and methyl 3,3,3-trifluoropyruvate using a rare carbonyl-yne reaction.[22] In turn, propargylation or allylation of the hydroxyl group would give rise to carbocyclization precursors yne-allene **8** or ene-allene **9** (eq 1). Moreover, the presence of the methyl ester provides a functional group that can be easily diversified and the trifluoromethyl group was known to have unique properties, such as high electronegativity, electron density, steric hindrance, and hydrophobicity.[23]



(1)

Feasibility studies began in order to establish the synthetic viability of methyl 2-(trifluoromethyl)-2-hydroxyalkadienoate **7** as a suitable substrate for diversification. The low reactivity of an alkyne in a carbonyl-yne reaction requires the use of "superenophiles".[24] Examples other than the carbonyl-yne reaction reported by Burger are known,[25] but his protocol proved most amenable to our needs. The thermal carbonyl-yne reaction of 1-hexyne or 1-propyne with methyl 3,3,3-trifluoropyruvate **10** gave racemic methyl 3,3,3-trifluoromethylocta-3,4-dienoate **11** (R = propyl) as a 1:1 mixture of diastereomers of methyl 3,3,3-trifluoromethylpenta-3,4-dienoate **11** (R = H); Burger also showed that effecting the former reaction using a Lewis-acid mediated protocol (3 equiv of $MgBr_2$) produced the same allene in 90% yield in an 8:1 mixture (eq 2). Thus, we explored the scope of Burger's *thermal* carbonyl-yne reaction by using microwave heating. (While the higher diastereoselectivity of the Lewis-acid catalyzed carbonyl-yne reaction was considered, the quantity of $MgBr_2$ (3 equiv relative to the pyruvate) and the quantity of solvent (0.06 M in CH_2Cl_2) made this protocol less amenable to scale-up.)



(2)

Indeed, heating 1-hexyne and methyl 3,3,3-trifluoropyruvate at 125 °C in a Biotage Emrys Optimizer microwave reactor gave the allene **11**{*1*} in 85% yield (entry a, Table 1) in 45 min (compared to 48 h at 80 °C using traditional heating in a sealed tube). Moreover, the microwave-assisted reactions required only 2 equiv of alkyne (compared to 3 equiv for Burger's conditions). In this case involving a volatile alkyne, it was observed that the pressure of the microwave decreased when the reaction was in progress and stabilized when the reaction was complete. A variety of alkynes were subjected to the microwave-assisted carbonyl-yne reaction conditions and the results are depicted in Table 1. The allene-forming reaction proved to be tolerant to a variety of functional groups such as an aryl group (entry b), a *t*-butyl silyl (TBS) ether (entry c), a nitrile (entry f), an alkyl chloride (entry g), and a carboxylic acid (entry h). Surprisingly, under the thermal conditions, the aryl allene **11**{*2*} did not undergo an isomerization reaction to give the conjugated styrene. An additional alkyl group at the homopropargylic position provided the corresponding allenes **11**{*4*} and **11**{*5*} (entries d and e). However, an extra alkyl group at the propargylic position gave only the butadienyl product **11**{*9*} (entry i). 1-Butyne gas was also used to prepare the 3,4-hexadienoates **11**{*10*} and **11**{*11*} (entries j and k). In the case of a symmetrical internal alkyne, the corresponding trisubstituted allene **11**{*12*} was isolated in high yield (entry l). It was anticipated that a mixture of products would be obtained if the internal alkyne was unsymmetrical, so these alkynes were not examined. Interestingly, the reaction of propargyl bromide gave the bromoallene **11**{*13*}, albeit in very low yield (entry m).

While the carbonyl-yne reaction was general for a variety of alkynes and proceeded in excellent yields, the subsequent O-alkylation of the tertiary alcohols proved to be problematic

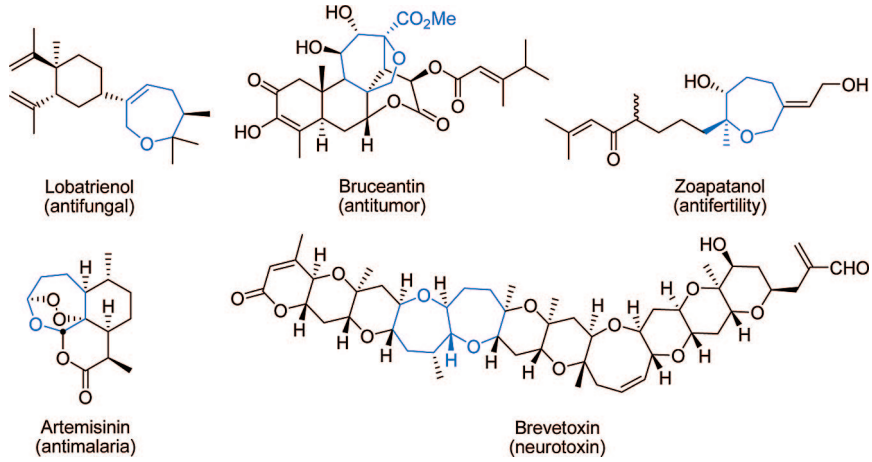
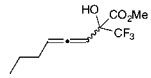
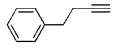
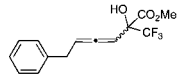
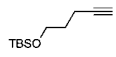
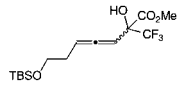
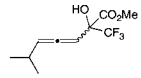
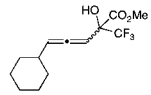
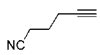
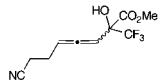
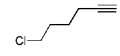
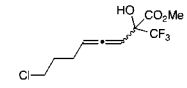
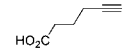
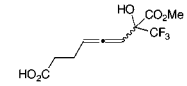
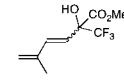
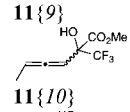
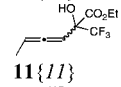
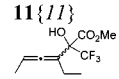
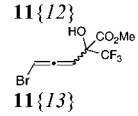


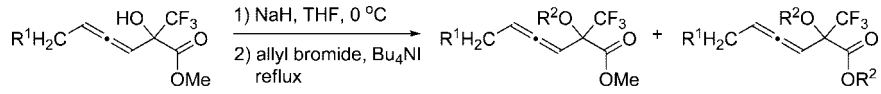
Figure 2. Biologically relevant oxepines and oxepanes.

Table 1. Microwave-Assisted Carbonyl-yne Reaction

Entry	Alkyne	Product	Yield
a		 **11**{*1*}	85%
b		 **11**{*2*}	90%
c		 **11**{*3*}	85%
d		 **11**{*4*}	57%
e		 **11**{*5*}	72%
f		 **11**{*6*}	70%
g		 **11**{*7*}	73%
h		 **11**{*8*}	70%
i		 **11**{*9*}	72%
j		 **11**{*10*}	51%[a]
k		 **11**{*11*}	58%[a]
l		 **11**{*12*}	71%[b]
m		 **11**{*13*}	18%

[a] A large excess of 1-butyne was used. [b] The temperature was held at 190 °C for 1 h.

Scheme 1. O-Allylation of Tertiary Alcohols **11**{*1–3*}



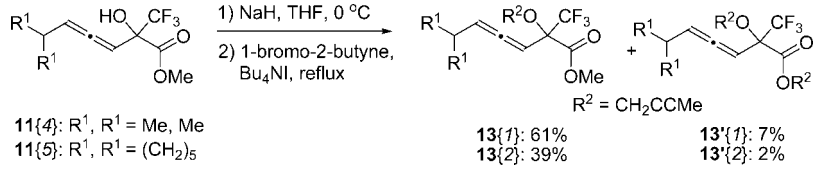
11{*1*}: R^1 = Et
11{*2*}: R^1 = Ph
11{*3*}: R^1 = CH_2OTBS

12{*1*}: 50% **12'**{*1*}:12%
12{*2*}: 44% **12'**{*2*}: 8%
12{*3*}: 63% **12'**{*3*}: 7%

(Scheme 1). It had previously been shown that O-alkylation of tertiary alcohols with an α-trifluoromethyl group required catalytic tetrabutylammonium iodide and refluxing THF and only provided moderate yields of the alkylation product.[26] Using this technique, we were able to achieve O-allylation of **11** with allyl bromide. However, in addition to the O-allylation product **12**, these reactions also yielded a transesterification product, giving the allyl ester **12′**. The ratios were substrate dependent, but were reproducible, varying from 9 to 4:1 in favor of the methyl ester (Scheme 1). Addition of water greatly increased the amount of the transesterification product **12′**; however, addition of activated molecular sieves had no effect, nor did switching from the methyl ester **11**{*10*} to the ethyl ester **11**{*11*}. The transesterification was thought to arise from a hydrolysis of the methyl ester followed by an allylation to give **12′**. However, no intermediate carboxylic acid was isolated. Because the esters would ultimately be used as a diversity subunit, we opted to proceed forward with library synthesis with the mixture of **12** and **12′**.

Similarly, when tertiary alcohols **11**{*4,5*} were allowed to react with 1-bromo-2-butyne, again the desired **13**{*1,2*}

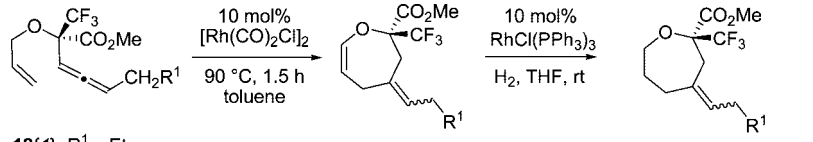
Scheme 2. O-Propargylation of Tertiary Alcohols **11**{*4*,*5*}



11{*4*}: R^1, R^1 = Me, Me
11{*5*}: R^1, R^1 = $(CH_2)_5$

13{*1*}: 61% **13**{*2*}: 39% **13′**{*1*}: 7% **13′**{*2*}: 2%

Scheme 3. Rh(I)-Catalyzed Carbocyclization Reaction Affording Racemic Oxepines



12{*1*}: R^1 = Et
12{*2*}: R^1 = Ph
12{*3*}: R^1 = CH_2OTBS

14{*1*}: 77% (*E*:*Z* = 1:2.8)
14{*2*}: 54% (*E*:*Z* = 1:3.5)
14{*3*}: 60% (*E*:*Z* = 1:1.9)

15{*1*}: 81% (*E*:*Z* = 1:5.4)
15{*2*}: 65% (*E*:*Z* = 1:4.7)
15{*3*}: 71% (*E*:*Z* = 1:3.2)

was obtained together with the transesterification byproduct **13′**{*1,2*} (Scheme 2). These esters were moved to the next step as mixtures.

Scaffold Generation: Phase I of Library Preparation. We previously reported a Rh(I)-catalyzed Alder-ene reaction of an ene-allene to generate tetrahydroazepines (Figure 1, **1** → **6**).[12c] The efficiency of this reaction was dependent upon the substituents on the allene. For example, terminal allenes gave only decomposition products, but the placement of a *t*-butyl or trimethylsilyl (TMS) group on the allene terminus gave high yields of the corresponding carbocyclization products. This report also included two examples of oxepine formation from the corresponding allyl ethers. In these two cases, the yields were moderate (40% and 55%), but this was attributed to the volatility of the products. In the context of the synthesis of a library of compounds, we were interested in using this carbocyclization process to prepare a novel scaffold, resembling the monocyclic natural products shown in Figure 2. The carbocyclization precursors **12** were chosen to maximize diversity on the exocyclic double bond of the oxepine **14**. Thus, substrates possessing an alkyl, benzyl, and TBS-protected ethanol were subjected to the Rh(I)-catalyzed carbocyclization conditions. In each case, the cyclization reactions were facile (1.5 h at 90 °C) and provided good yields of the corresponding oxepines. It was found that 4-methylene-2,3,4,5-tetrahydrooxepines **14**{*1–3*} were not stable at room temperature for prolonged periods, probably because of the enol ether moiety. Therefore, in order to access more stable scaffolds, two different hydrogenation protocols were applied to reduce the enol ether double bond. Subjecting 4-methylene-2,3,4,5-tetrahydrooxepines **14**{*1–3*} to Wilkinson's catalyst, the enol ether double bond was reduced selectively with the trisubstituted double bond intact. The *E* and *Z* ratio ranges from 1:3.2 to 1:5.4 with the yield ranging from 65% to 81% (Scheme 3). The *E*/*Z* stereochemistry was assigned based upon near Overhauser effect (NOE) measurements of a later compound **19**{*4,1*} (vide infra). The differences in the *E*/*Z* ratio between **14** and **15** are due to a selective removal of the *E* isomer during column chromatography.

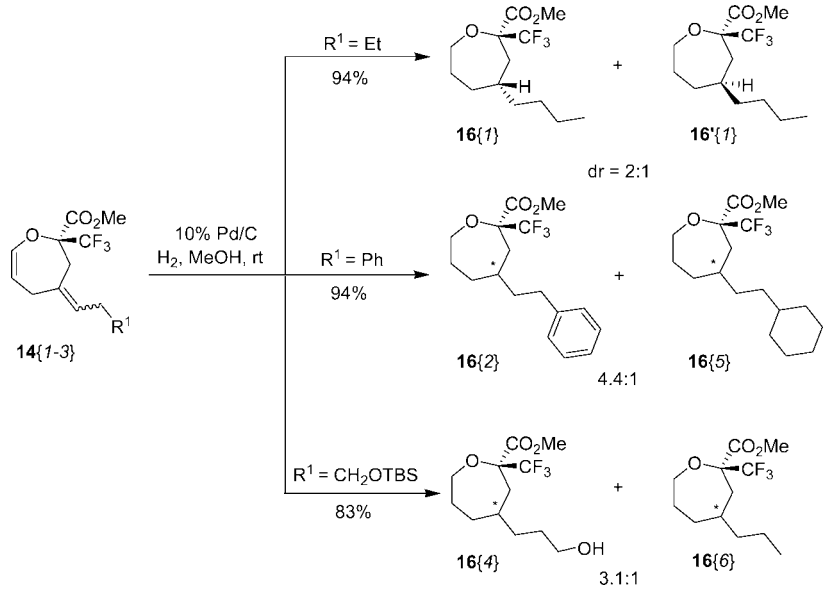
On the other hand, reaction of 4-methylene-2,3,4,5-tetrahydrooxepines **14**{*1–3*} using 10% Pd/C and H_2 provided the fully saturated oxepanes **16**{*1–2,4–6*}. Reduction of **14**{*1*} cleanly gave two diastereomers of **16**{*1*} in a 2:1 ratio. However, reduction of **14**{*2*} afforded a mixture of **16**{*2*} and the cyclohexyl analog **16**{*5*}, resulting from overreduction of the phenyl group of **16**{*2*}. Oxepene **14**{*3*} gave oxepanes **16**{*4*} and **16**{*6*}. The former is a result of a reduction and simultaneous removal of the TBS protecting group. The latter presumably results from the elimination of the TBS group followed by double bond reduction or a hydrogenolysis process (Scheme 4). The ratio of intermediates **16**{*2,4–6*} was not determined at this stage. In addition, **16**{*2*} and **16**{*5*} as well as **16**{*4*} and **16**{*6*} were used as mixtures in the subsequent reactions, and the structures were characterized after the amidation step.

Next, subjecting allene-ynes **13**{*1,2*} to the Rh(I)-catalyzed carbocyclization process provides pyran containing scaffolds **17**{*1,2*} in 93% and 95% yield, respectively, in less than 5 min at room temperature (Scheme 5). The substituents on the terminus of the appended double bond of the pyran skeleton were selected to (a) limit the number of olefin stereoisomers and (b) decrease its reactivity as a diene by sterically forcing this double bond out of conjugation with the internal double bond.

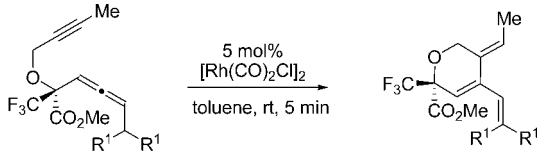
Thus, unique scaffolds have been generated using a dual-branching strategy: a moderately flexible alkylideneoxepane scaffold **15**{*1–3*}; a very flexible alkyloxepane scaffold **16**{*1–2,4–6*}; and a relatively rigid tetrahydropyran scaffold **17**{*1–2*} (Figure 3).

Scaffold Functionalization: Phase II of Library Preparation. With **15**{*1–3*}, **16**{*1–2,4–6*}, and **17**{*1–2*} in hand, our next goal was to establish an appendage substitution pattern that would lead not only to novel compounds but also to compounds that have a satisfied druglike physicochemical profile. Currently, each scaffold possesses a methyl 3,3,3-trifluoromethyl-carboxylate-ether functionality and a lipophilic or polar R^1 handle. Thus, in order to better satisfy this physicochemical profile and to synthesize a library of versatile analogs, we elected to transform the methyl ester to the corresponding amides applying a set of thirteen primary amines **18**{*1–13*} (Figure 4). Methylamine **18**{*1*} was chosen because of its small size, and cyclopropylmethylamine **18**{*2*}, because of its lipophilic character, while amines **18**{*3–4*} were examples for more polar aliphatic building blocks. *N*-(Aminoethyl)-morpholine **18**{*5*} was appealing because of its basic nitrogen, and amines **18**{*6–7*} were interesting because of their ability to function as hydrogen bond donors. The list of aromatic amines contained

Scheme 4. Palladium-Catalyzed Hydrogenation Affording Fully Saturated Racemic Oxepanes



Scheme 5. Rh(I)-Catalyzed Carbocyclization Reaction Affording Racemic Pyrans



benzylamine **18**{*8*} as well as electron-deficient (**18**{*9*}) and electron-rich benzylamines (**18**{*10*}) and three heteroaromatic isosteres (**18**{*11–13*}).

Physicochemical Profiling. Three-dimensional (3D) structures of all library members **19**{*1–2*,4;*1–13*}, **20**{*1–2*,*4–6*; *1–13*}, and **21**{*1–2*;*1–13*} (Schemes 6−8) were built and minimized using the MM2 force field in Macro Model 8.6. The physiochemical profiling of the 90 library members was analyzed computationally using QikProp 2.1.[27] All molecular descriptors show values well within the range that is considered to be druglike[28] (Table 2).

Library Synthesis. The synthesis of alkylidene-oxepanecarboxamides **19**{*1–2*,*4*; *1–13*} (Scheme 6) started with the saponification of the methyl esters **15**{*1–3*} by 3 equiv of LiOH in the case where R^1 is an ethyl or a phenyl group. When R^1 is a TBS-protected alcohol **15**{*3*}, the TBS group was first removed by TBAF, and then saponification followed to give **15**{*4*}. In all cases after saponification, the crude mixture was diluted with H_2O and the resulting mixture was extracted with EtOAc to remove any organic impurities. The separated aqueous phase was then acidified to pH 2 and extracted with EtOAc. After concentration, the crude carboxylic acid was obtained and used without further purification. With crude carboxylic acid in hand, amidation was carried out with 2 equiv of polymer-bound carbodiimide (PS-DCC), 1.5 equiv of 1-hydroxybenzotriazole (HOBt), and 5 equiv of primary amines **18**{*1–13*} using an automated Biotage Emrys Optimizer microwave reactor. The reaction mixture was irradiated at 100 °C for 10 min except for methylamine **18**{*1*} and cyclopropanemethylamine **18**{*2*}. Due to their low boiling point, 25 equiv of **18**{*1*} and **18**{*2*} were added and allowed to react at 60 °C for 40 min. After all the reactions were complete, excess reagents and polymer beads were removed by filtration through a silica-bound carbonate cartridge in a parallel fashion. Then, all the filtrates were concentrated in an HT-4 Genevac evaporator. Since excess amines cannot be removed by filtration, further silica gel flash chromatography was carried out in an ISCO Optix

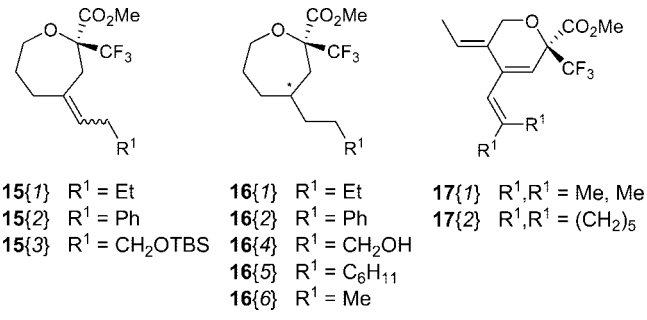


Figure 3. Building blocks **15**{*1–3*}, **16**{*1*−*2*,*4–6*}, and **17**{*1–2*}.

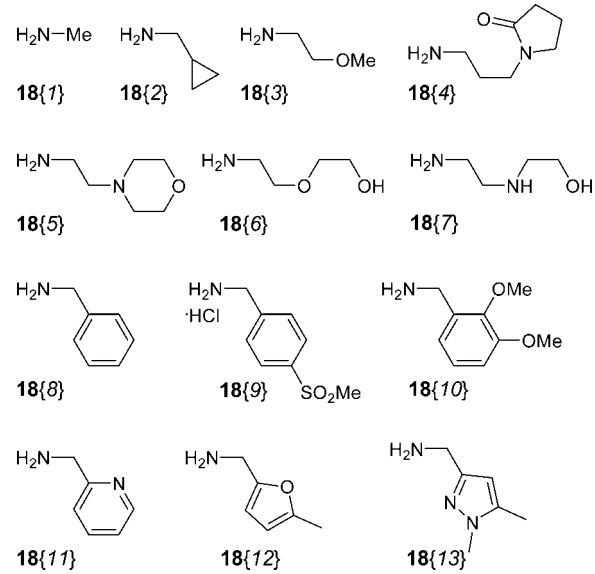
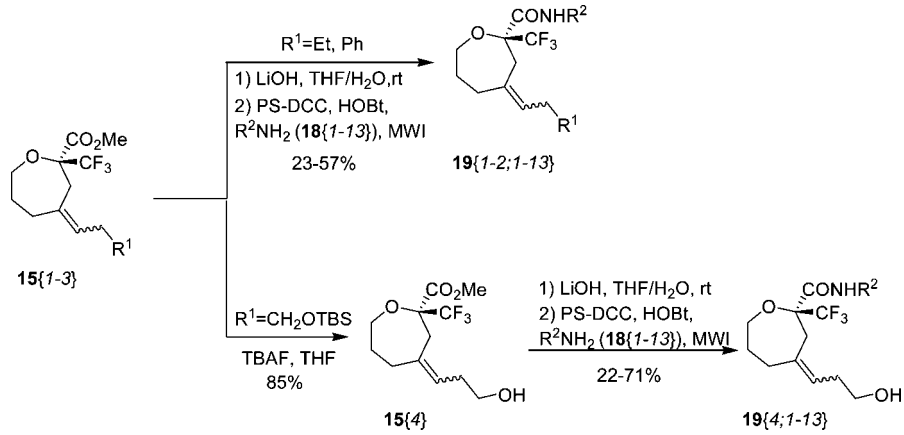
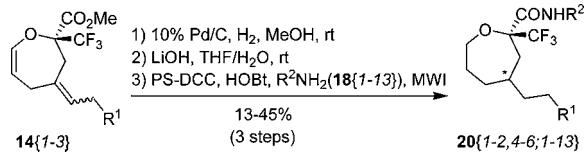


Figure 4. Building blocks **18**{*1–13*}.

Scheme 6. Synthesis of Alkylidene-oxepanecarboxamides **19**{*1–2,4*;*1–13*}



Scheme 7. Synthesis of Alkyl-oxepanecarboxamides **20**{*1–2,4–6*;*1–13*}



Scheme 8. Synthesis of Carboxamides **21**{*1–2*;*1–13*}

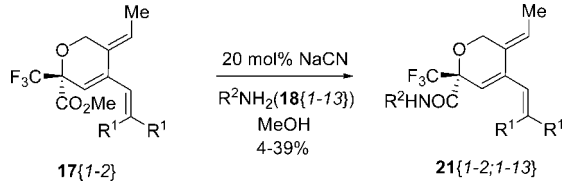


Table 2. Physicochemical Data of Cyclic Ether Library (Calculated with QikProp 2.1[27]) Compared with Drug Likeness[27,28]

property	average value ± standard deviation	range for 95% drug likeness
MW	379 ± 47	130–725
HBD	1.34 ± 0.62	0–6
HBA	5.49 ± 1.61	2–20
log P	3.54 ± 1.20	−2 to 6
log S	−3.99 ± 1.36	−6 to 0.5
rotatable bonds	6.10 ± 1.45	0–15
log Khsa	0.15 ± 0.43	−1.5 to 1.2
Caco-Perm. [nm/s]	3113 ± 2080	25 poor, 500 great

10 system eluting with hexane and EtOAc. The yields obtained for amides **19**{*1–2,4*;*1–13*} ranged from 22% to 71% over two steps including saponification and amidation with an average amount of 33 mg. Direct displacement of the methyl ester by amines gave low yield of the amides. The stereochemistry of the exocyclic double bond was determined based on NOE results (Figure 5). Irradiation of Ha (δ 3.52 ppm) in *Z*-**19**{*1,4*} showed that there is no NOE effect on Hb (δ 5.44 ppm). On the other hand, irradiation of Ha (δ 3.52 ppm) in *E*-**19**{*1,4*} showed 7% NOE effect between Ha (δ 3.52 ppm) and Hb (δ 5.33 ppm).

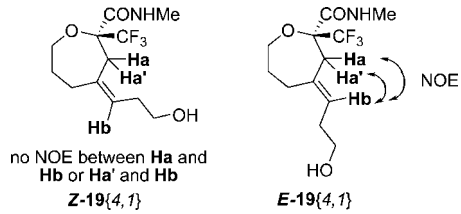


Figure 5. Stereochemistry determination based on NOE experiment on compound **19**{*4,1*}.

Synthesis of alkyl-oxepanecarboxamides **20**{*1–2,4–6*;*1–13*} (Scheme 7) was carried out using the same saponification and microwave-assisted amidation protocol as described above. The yields ranged from 13% to 45% over three steps including palladium-catalyzed hydrogenation, saponification, and amidation. The average amount obtained was 23 mg. The stereochemistry of the major diastereomer was confirmed by X-ray crystallography for compound **20**{*1*, *8*} as shown in Figure 6.

Carboxylic esters **17**{*1–2*} were converted to carboxamides **21**{*1–2*;*1–13*} using a NaCN-catalyzed protocol that directly transforms esters to amides as shown in Scheme 8. Attempts to affect the ester saponification followed by amidation protocol as used before gave low yield and decomposition products. The yields ranged from 4% to 39%, and the average amount obtained was 18 mg.

Purity Analysis. All library members were submitted to LC/MS/ELSD analysis for evaluation of their purities. Ninety compounds showed purity above 90%, and seven compounds had purities less than 90% and had to be repurified. The details of each compound's purity are listed in Table 3.

Diversity Analysis. A diversity analysis was performed on the library of 90 cyclic ethers by combining cell-based chemistry-space computations using BCUT (Burden (B) CAS (C) Pearlman at the University of Texas (UT)) metrics and Tanimoto coefficient (Tc) similarity calculations using two-dimensional (2D) fingerprints,[29] revealing that these compounds fill voids in chemical space when compared to the existing PMLSC[30] compound library and the PubChem[31] database. Chemistry space composed of molecular BCUT matrix values[32] and a binning procedure were used to generate cells for compound partitioning from a multidimensional original descriptor space,[33] and illustrated in Figure 7 are the results of the comparison of the newly

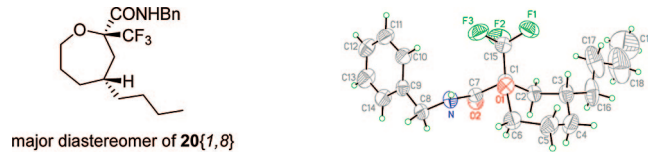


Figure 6. Structure and X-ray of compound **20**{*1,8*}.

Table 3. Library Matrix for **19**{*1–2,4*;*1–13*}, **20**{*1–2,4–6*;*1–13*}, and **21**{*1–2*;*1–13*}[d]

R^2	**19**{*1,1-13*}	**19**{*2,1-13*}	**19**{*4,1-13*}	**20**{*1,1-13*}	**20**{*2,1-13*}	**20**{*4,1-13*}	**21**{*1,1-13*}	**21**{*2,1-13*}
18{*1*}	**19**{*1,1*} 27 (98[c])	**19**{*2,1*} 37 (>99)	**19**{*4,1*} 71 (>99)	**20**{*1,1*} 29 (90[c])	**20**{*2,1*}[a] 19 (>99)	**20**{*4,1*} 16 (>99)	-	**21**{*2,1*} 17 (98)
18{*2*}	**19**{*1,2*} 30 (>99)	**19**{*2,2*} 40 (>99)	**19**{*4,2*} 38 (>99)	**20**{*1,2*} 26 (>99)	**20**{*2,2*}[a] 20 (98)	**20**{*4,2*} 39 (>99)	-	-
18{*3*}	**19**{*1,3*} 49 (95)	**19**{*2,3*} 44 (97)	**19**{*4,3*} 70 (>99)	**20**{*1,3*} 13 (>99)	-	**20**{*4,3*} 30 (>99)	-	-
18{*4*}	-	-	-	-	-	-	**21**{*1,4*} 24 (94)	-
18{*5*}	**19**{*1,5*} 23 (>99)	**19**{*2,5*} 36 (>99)	**19**{*4,5*} 65 (>99)	**20**{*1,5*} 24 (>99)	**20**{*2,5*} 15 (>99)	**20**{*4,5*}[b] 30 (>99)	**21**{*1,5*} 11 (100)	**21**{*2,5*} 15 (100)
18{*6*}	-	-	-	-	-	-	**21**{*1,6*} 25 (94)	**21**{*2,6*} 13 (99)
18{*7*}	**19**{*1,7*} 35 (>99)	**19**{*2,7*} 38 (>99)	**19**{*4,7*} 66 (>99)	**20**{*1,7*} 31 (>99)	**20**{*2,7*} 20 (>99)	-	-	-
18{*8*}	**19**{*1,8*} 50 (>99)	**19**{*2,8*} 56 (>99)	**19**{*4,8*} 67 (>99)	**20**{*1,8*} 33 (>99)	**20**{*2,8*}[a] 35 (>99)	**20**{*4,8*} 36 (>99)	**21**{*1,8*} 39 (94)	**21**{*2,8*} 26 (100)
18{*9*}	**19**{*1,9*} 46 (>99)	**19**{*2,9*} 39 (>99)	**19**{*4,9*} 22 (>99)	**20**{*1,9*} 31 (>99)	**20**{*2,9*}[a] 26 (90[c])	**20**{*4,9*}[b] 34 (90[c])	-	-
18{*10*}	-	-	-	-	-	-	**21**{*1,10*} 39 (100)	**21**{*2,10*} 39 (99)
18{*11*}	**19**{*1,11*} 57 (>99)	**19**{*2,11*} 35 (97)	**19**{*4,11*} 43 (>99)	**20**{*1,11*} 38 (>99)	**20**{*2,11*} 31 (>99)	**20**{*4,11*}[b] 27 (>99)	**21**{*1,11*} 4 (92)	-
18{*12*}	**19**{*1,12*} 56 (>99)	**19**{*2,12*} 36 (99)	**19**{*4,12*} 48 (>99)	**20**{*1,12*} 45 (>99)	**20**{*2,12*} 33 (97)	-	-	-
18{13}	**19**{*1,13*} 49 (>99)	**19**{*2,13*} 36 (>99)	**19**{*4,13*} 56 (>99)	**20**{*1,13*} 35 (>99)	**20**{*2,13*}[a] -	**20**{*4,13*}[b] 18 (>99)	-	-

[a] Byproducts **20**{*5,1*}, **20**{*5,2*}, **20**{*5,8*}, **20**{*5,9*}, and **20**{*5,13*} were isolated in yields from 11% to 13%. [b] Byproducts **20**{*6,5*}, **20**{*6,9*}, **20**{*6,11*}, and **20**{*6,13*} were isolated in yields from 21% to 24%. [c] Estimated purity by ^{1}H NMR. [d] Isolated yield (%); purity by ELSD (%).

synthesized library and PMLSC compound database.[34] The chemistry-space coordinates of the 90 cyclic ethers (red dots) are clustered in void regions of the PMLSC library (100 000 compounds in blue dots) in the 3D matrix plots.

Further studies were carried out analyzing and comparing three closely clustered regions (red dots), or voids filled by newly synthesized cyclic ether compounds. As shown in Figure 7, each dot represents a compound chemistry space matrix calculated by cell-based BCUT metrics algorithm. The three localized matrix regions (red dots) indicate that these synthetic compounds are partitioned in different cells based on their BCUT calculated molecular descriptor matrices (i.e., charge, H-bonding, or hydrophobic properties). A representative structure (compounds **1**, **2**, or **3**) is taken from each region, respectively. Compounds **1** and **4** are from the closest cluster region (the lower right area). 2D fingerprint Tanimoto coefficient values (Tc) are also provided for comparisons among these four compounds in Figure 7, showing that the three cyclic

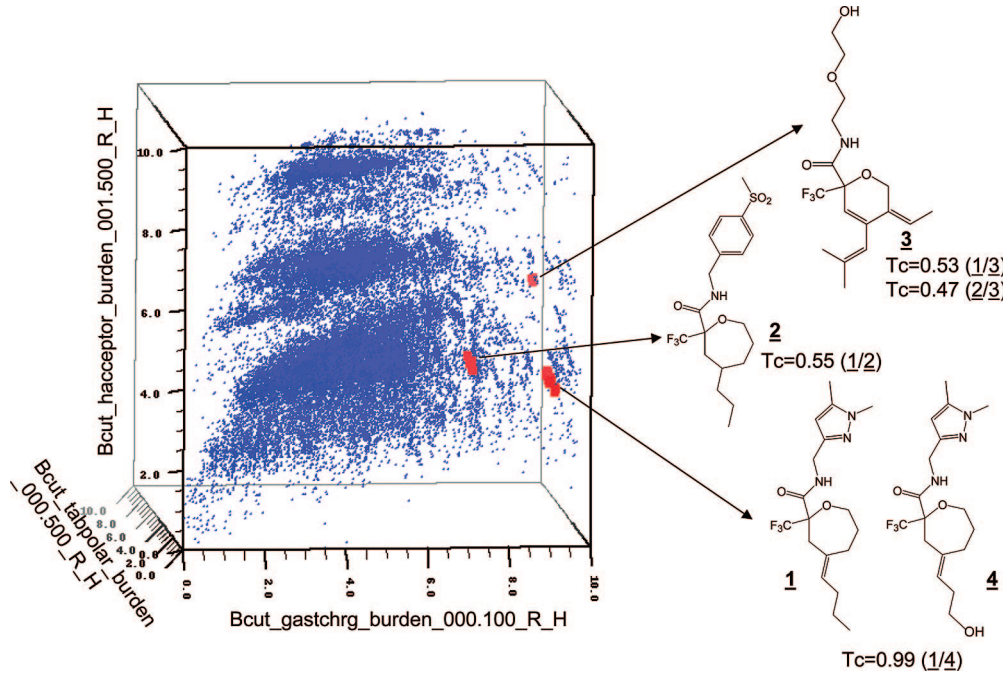


Figure 7. 3D chemistry-space matrix plots of synthesized 90 cyclic ether library (red dots) and 100 000 PMLSC compound database (blue dots) by cell-based diversity analysis using BCUT metrics calculation. The new compounds clearly fill the diversity voids of the current 100 000 compound database. One representative structure (compounds **1, 2,** and **3**) is retrieved from each cluster region (red dots), respectively, and shown on the left side. The compounds **1** and **4** are from a closest cluster region. Tanimoto coefficient values are calculated by the 2D fingerprint approach for comparisons among these four compounds.

ether derivatives **1**, **2**, and **3** have some differences in their structures with Tc values ranging from 0.47 to 0.55 whereas compounds **1** and **4** are quite similar (Tc = 0.99). The two computational results are congruent, and thus, combining these approaches provides us with a better understanding of the cyclic ether library in terms of its diversity and similarity properties.

In addition, a pairwise similarity comparison was conducted to evaluate the similarity properties of the cyclic ether library versus the entire PubChem database by using a 2D fingerprint Tanimoto coefficient (Tc) calculation. The results of the compound similarity comparison are given in Figure 8, revealing that none of the compounds in the two databases possess a pairwise Tc value higher than 0.75, a threshold for compound similarity comparison.[29] Actually, the compound percentage Gaussian distribution histogram (black curve) of the Tanimoto indices reveals a small mean value of 0.34 with a standard deviation of 0.06, which captures the scope of chemical diversity of the synthetic compound database, i.e., the smaller the mean Tc, the greater the range of database structure diversity in comparison with the PubChem database. Again, the compound cumulative percentage histogram (red curve) also shows Tc value of 0.63 at 100%, depicting that all compounds in the cyclic ether library are novel with respect to the PubChem database. The results further confirm that the newly synthesized cyclic ether library improves the quality of existing compound databases by enriching the compound diversity.

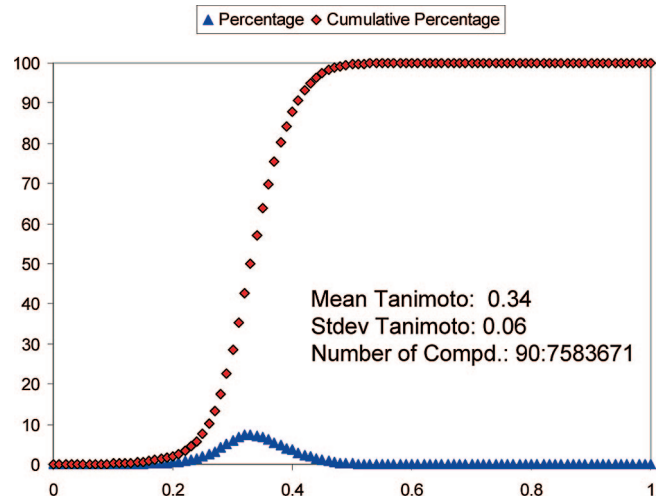


Figure 8. Database similarity plots of the calculated Tanimoto coefficients (Tc) versus the correspondent percentage compound population by comparing the synthesized compound library with the PubChem compound database (7.58 million compounds filtered with MWs under 800). Tc values were calculated with a pairwise 2D fingerprint metrics method. A low mean Tc indicates a low degree of similarity of the compounds between the synthesized compound database and the PubChem compound database.

Conclusion

In the present study, we have demonstrated that a common intermediate either an allenyl allyl ether or an allenyl propargyl ether can be transformed into two scaffolds either oxepines or pyrans using Rh(I)-catalyzed carbocyclization conditions. The oxepine scaffold was further reacted under two complementary hydrogenation conditions to provide two new scaffolds with an α-alkoxy ester moiety, which were applied to a library synthesis of alkyl- and alkylideneoxepanecarboxamides. A microwave-assisted amidation protocol using polymer bound DCC and HOBt was used to make the process more efficient. The pyran scaffold that contains an α-alkoxy ester was transformed into carboxamides via a NaCN-catalyzed aminolysis process. Compounds were obtained in quantities ranging from 3 to 58 mg each with an average purity of 98% (LC/MS/ELSD). A diversity analysis

shows that these compounds occupy unique chemical space. Biological evaluations of these compounds are ongoing, and the results can be accessed in PubChem (http://pubchem.ncbi.nlm.nih.gov).

Experimental Section

General. All air and moisture sensitive reactions were performed under an argon atmosphere. THF was purified by distillation from Na/benzophenone. Toluene and CH_2Cl_2 were purified by filtration through activated alumina. Chemicals were obtained from Acros, Aldrich Chemical Co, GFS Chemicals, or Matrix Scientific and used as received. The rhodium biscarbonyl chloride dimer was obtained from Strem Chemicals. Polymer-bound carbodiimide (PS-DCC) was purchased from Argonaut, and silica-bound carbonate solid phase extraction (SPE) cartridges were from Silicycle. Other solvents or reagents were used without further purification. NMR spectra were recorded in $CDCl_3$ (298 K) at 300.1 (^{1}H), 75.5 (^{13}C), or 282.3 MHz (^{19}F) using a Bruker Avance 300 with Topspin software. Chemical shifts (δ) are reported in parts per million (ppm). Chloroform-*d* was used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), integration and coupling constants. IR spectra were obtained on a Nicolet AVATAR 360 FTIR ESP spectrometer. Mass spectra were obtained on a Waters QtoF API US. Melting points were obtained using a heating rate of 2 °C/min on a MelTemp melting point apparatus with digital temperature reading and are reported uncalibrated. All microwave-assisted reactions were performed in a Biotage Emrys Optimizer microwave reactor or a CEM Discover microwave reactor. Chromatography was performed using either a Biotage Horizon chromatography system or an ISCO CombiFlash Companion system.

Compounds were analyzed by reverse-phase HPLC (Alltech Prevail C-18, 100 × 4.6 mm, 1 mL/min, CH_3CN, H_2O and 0.1% TFA) with UV (210, 220, and 254 nm), ELS (nebulizer 45 °C, evaporator 45 °C, N_2 flow 1.25 SLM), and MS detection using a Thermo Finnigan Surveyor LC and LCQ Advantage MS system (ESI positive mode).

General Procedure for Microwave-Assisted Carbonyl-yne Reaction to Provide 11{*1–13*}. A microwave reactor vial equipped with a stir bar was charged with methyl 3,3,3-trifluoropyruvate (0.21 mL, 2.0 mmol) and 1-hexyne (0.46 mL, 4.0 mmol). The vial was capped and placed in the Biotage Emrys Optimizer microwave reactor. The reaction mixture was irradiated at 125 °C for 45 min. Then volatile materials were removed by rotovap, and the crude product was purified by silica gel flash chromatography to give **11**{*1*} (0.41 g, 85%). The two diastereomers were inseparable, and the data is reported as a mixture of two diastereomers. The * symbol denotes the second diastereomer. The ratio of the two diastereomers was determined based on ^{1}H NMR integration of the OH resonance.

Methyl 2-(Trifluoromethyl)-2-hydroxyocta-3,4-dienoate (11{*1*}). Following the general procedure for microwave-assisted carbonyl-yne reaction, **11**{*1*} was obtained as a colorless oil as two diastereomers (3:2). ^{1}H NMR ($CDCl_3$) δ 5.61–5.53 (m, 1 H), 5.47–5.42 (m, 1 H), 3.92 (s, 9/5 H), *3.91 (s, 6/5 H), 3.84 (s, 1 H), *3.81 (s, 1 H), 2.10–2.00 (m, 2 H), 1.52–1.37 (m, 2 H), 0.97–0.91 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 194.6, 169.3, 123.1 (q, J_{CF} = 284.3 Hz), 97.9, *97.8, 88.2, 75.8 (q, J_{CF} = 30.0 Hz), 54.4, *54.3, 30.3, *30.0, 21.2, *21.1, 13.8; ^{19}F NMR ($CDCl_3$) δ −78.6 (s, 3 F), *−78.7 (s, 3 F); IR (film) 3486, 2963, 2937, 2877, 1971, 1750, 1440, 1299, 1243 cm^{-1}; MS (EI) *m/z* (rel. intensity) 238 (50), 221 (40), 181 (40), 169 (100), 141 (27), 59 (88); HRMS (EI) *m/z* calcd for $C_{10}H_{13}F_3O_3$ 238.0817, found 238.0813.

General Procedure for O-Allylation of 11{*1–3*}. A 50 mL three-neck flask was charged with NaH (0.50 g of a 60% dispersion in mineral oil, 19 mmol), followed by 10 mL THF to give a white emulsion. This mixture was cooled to 0 °C. In another 25 mL flask, 2-hydroxy-2-trifluoromethylocta-3,4-dienoic acid methyl ester **11** {*1*} (2.38 g, 10.0 mmol) was diluted in 10 mL THF to give a light yellow solution, which was then added dropwise to the cold NaH emulsion. After the addition was complete, the ice–water bath was removed and the reaction was run at rt for 30 min. Next, tetrabutylammonium iodide (0.92 g, 2.5 mmol) and allyl bromide (1.3 mL, 15 mmol) were added successively, and then, the mixture was placed into a preheated oil bath (65 °C). After refluxing for 15 h, the oil bath was removed and water was added slowly to the cooled reaction mixture. Then, Et_2O was added and the separated organic phase was washed with H_2O twice and brine once. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by silica gel flash chromatography to give **12**{*1*} (1.4 g, 50%) and **12′**{*1*} (0.35 g, 12%).

Methyl 2-(Allyloxy)-2-trifluoromethylocta-3,4-dienoate (12{*1*}). According to the general procedure for O-allylation, **12**{*1*} was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.01–5.88 (m, 1 H), 5.52–5.43 (m, 1 H), 5.37–5.31 (m, 2 H), 5.19 (d, 1 H, J = 10.5 Hz), 4.31–4.17 (m, 2 H), 3.83 (s, 1.5 H), *3.82 (s, 1.5 H), 2.12–2.00 (m, 2 H), 1.46 (sextet, 2 H, J = 7.5 Hz), 0.94 (t, 3 H, J = 7.5 Hz).

Allyl 2-(Allyloxy)-2-(trifluoromethyl)octa-3,4-dienoate (12′{*1*}). According to the general procedure for O-allylation, **12′**{*1*} was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.01–5.86 (m, 2 H), 5.51–5.11 (m, 6 H), 4.78–4.64 (m, 2 H), 4.32–4.20 (m, 2 H), 2.11–1.99 (m, 2 H), 1.45 (sextet, 2 H, J = 7.5 Hz), 0.94 (t, 3 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 196.7, 166.1, 134.2, 131.2, 123.1 (q, J = 284.3 Hz), 118.5, *118.4, 113.3, *113.2, 96.3, *96.1, 85.9, 67.9, 66.9, *66.8, 30.3, *29.9, 21.3, *21.2, 13.8, *13.8; ^{19}F NMR ($CDCl_3$) δ −75.8 (s, 1.5 F), −76.1 (s, 1.5 F); IR (film) 2961, 2929, 1356, 1278, 1234 cm^{-1}; MS (EI) *m/z* (rel. intensity) 263 (69), 149 (99), 91 (81), 79 (97), 69 (58), 55 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{14}F_3O_3$263.0895, found 263.0903.

General Procedure for O-Propargylation of 11{*4–5*}. To a flame dried threaded culture tube (13 × 100 mm) equipped with a stir bar was added NaH (90 mg, 3.8 mmol), followed by THF (2.8 mL). This was cooled to 0 °C. In another 5 mL flask, methyl 2-(trifluoromethyl)-2-hydroxy-6-methylhepta-3,4-dienoate **11**{*4*} (0.26 g, 1.1 mmol) diluted in 1.5 mL THF was added dropwise to the cold NaH emulsion. After gas evolution stopped, tetrabutylammonium iodide (99 mg, 0.22 mmol) was added all at once. Then 1-bromo-2-butyne (0.19 mL, 2.2 mmol) was added dropwise.

The mixture was placed into a preheated oil bath (80 °C). After refluxing for 4 h, the oil bath was removed and 10 mL Et_2O was added to the cooled reaction mixture, followed by 10 mL 0.5 M HCl. The separated organic phase was washed with H_2O (2 × 10 mL) and brine (1 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by silica gel flash chromatography to give **13**{*1*} (0.19 g, 61%).

Methyl 2-(But-2-ynyloxy)-6-methyl-2-(trifluoromethyl)hepta-3,4-dienoate (13{*1*}). According to the general procedure for O-propargylation, **13**{*1*} was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 5.54–5.40 (m, 2 H), 4.46–4.32 (m, 2 H), *3.82 (s, 1.5 H), 3.81 (s, 1.5 H), 2.41–2.35 (m, 1 H), 1.85 (t, 3 H, J = 2.2 Hz), 1.05 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 205.3, *166.4, 166.2, *103.4, 103.2, 86.4, 83.1, 74.6, 55.5, 52.9, 52.7, 27.8, 22.2, 22.0, 21.8, 3.7; IR (film) 2964, 2927, 2874, 1755, 1284, 1238 cm^{-1}.

General Procedure for Carbocyclization of 12{*1–3*}. A threaded culture tube (13 × 100 mm) was charged with methyl 2-(allyloxy)-2-trifluoromethyl-octa-3,4-dienoate **12**{*1*} (25 mg, 0.090 mmol) and toluene (0.9 mL) under argon to give a clear solution. Then rhodium biscarbonyl chloride dimer (3.5 mg, 0.0090 mmol) was added all at once to give a yellow solution. This solution was placed into a preheated oil bath (90 °C). After 1.5 h, the oil bath was removed. The cooled product was loaded onto a short silica gel pad and was first eluted with hexane followed by 10:1 hexane/EtOAc. The solvent was removed in vacuo to give methyl 4-butylidene-2-(trifluoromethyl)-2,3,4,5-tetrahydrooxepine-2-carboxylate **14**{*1*} (18 mg, 77%). Oxepine **14**{*1*} was taken on directly to the next step as a mixture of *E/Z* isomers, and the ratio was determined to be 1:2.8 (*E/Z*) based on the ^{1}H NMR integration of the vinyl proton resonance. The *E/Z* isomers were inseparable using silica gel flash chromatography; the data is reported as a mixture of *E/Z* isomers, and * denotes the *E* isomer.

Methyl 4-Butylidene-2-(trifluoromethyl)-2,3,4,5-tetrahydrooxepine-2-carboxylate (14{*1*}). According to the general procedure for carbocyclization, **14**{*1*} was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.27 (d, 1 H, J = 6.9 Hz), 5.39 (t, 0.67 H, J = 7.2 Hz), *5.33 (t, 0.33 H, J = 7.2 Hz), 4.96–4.90 (m, 1 H), 3.81 (s, 3 H), 3.38 (d, 1 H, J = 14.6 Hz), 3.01–2.92 (m, 1 H), 2.83 (d, 1 H, J = 5.1 Hz), 2.68 (d, 1 H, J = 14.6 Hz), 2.09–1.92 (m, 2 H), 1.42–1.24 (m, 2 H), 0.92 (t, 3 H, J = 7.5 Hz).

General Procedure for Hydrogenation of 14{*1–3*} using Wilkinson's Catalyst. A 5 mL flask equipped with a stir bar was charged with methyl 4-butylidene-2-(trifluoromethyl)-2,3,4,5-tetrahydrooxepine-2-carboxylate **14**{*1*} (21 mg, 0.079 mmol) and THF (0.8 mL) under argon. Then, Wilkinson's catalyst $RhCl(PPh_3)_3$ (8.4 mg, 9.0 μmol) was added all at once. The flask was evacuated twice under reduced pressure, and a H_2 balloon was placed on the top. After stirring at rt for 4 h, the solvent was removed and the crude product was purified by silica gel flash chromatography. 4-Butylidene-2-trifluoromethyl-oxepane-2-carboxylic acid methyl ester **15**{*1*} (17 mg, 81%) was obtained as a mixture of *E/Z* isomers and the ratio was determined to be 1:5.4 (*E/Z*) based on the ^{1}H NMR integration of the vinyl proton resonance. The *E/Z* isomers were inseparable using silica gel flash chromatography; the data is reported as a mixture of *E/Z* isomers, and * denotes the *E* isomer.

4-Butylidene-2-trifluoromethyl-oxepane-2-carboxylic acid methyl ester (15{*1*}). According to the general procedure for hydrogenation using Wilkinson's catalyst, **15**{*1*} was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 5.39 (t, 1 H, J = 7.2 Hz), *5.28 (t, 1 H, J = 7.5 Hz), 4.07–4.03 (m, 2 H), 3.82 (s, 3 H), *3.81 (s, 3 H), 3.11 (d, 1 H, J = 15.0 Hz), *2.97 (d, 1 H, J = 14.4 Hz), 2.73 (d, 1 H, J = 15.0 Hz), 2.31–2.12 (m, 2 H), 2.05–1.84 (m, 2 H), 1.82–1.68 (m, 2 H), 1.40–1.26 (m, 2 H), 0.90 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 168.5, *168.1, 131.7, *131.4, 131.1, 124.2 (q, J_{CF} = 285.8 Hz), 82.5 (q, J_{CF} = 27.0 Hz), *67.8, 67.7, 53.3, *53.0, 39.2, *39.1, 32.2, 30.5, *30.1, 30.0, *29.6, 23.0, *21.0, 13.9, *13.8; ^{19}F NMR ($CDCl_3$) δ −77.3 (s, 3 F); IR (film) 2960, 2934, 1347, 1438, 1308, 1288 cm^{-1}; MS (EI) *m/z* (rel. intensity) 280 (27), 237 (60), 109 (40), 95 (73), 81 (82), 67 (100), 55 (69); HRMS (EI) *m/z* calcd for $C_{13}H_{19}F_3O_3$ 280.1286, found 280.1288.

General Procedure for Palladium Catalyzed Hydrogenation of 14{*1–3*}. A 100 mL flask equipped with a stir bar was charged with methyl 4-butylidene-2-(trifluoromethyl)-2,3,4,5-tetrahydrooxepine-2-carboxylate **14**{*1*} (0.86 g, 3.1 mmol) and MeOH (19 mL) to give a colorless solution under argon. Then 10% Pd/C (0.33 g, 0.31 mmol) was added in three portions under argon. The reaction flask was evacuated twice under reduced pressure, and a H_2 balloon was placed on the top. After stirring at rt for 8 h, the mixture was filtered through Celite and the filtrate was concentrated in vacuo to give 4-butyl-2-trifluoromethyloxepane-2-carboxylic acid methyl ester **16**{*1*} (0.82 g, 94%) as two diastereomers, and the ratio was determined to be 2:1 based on the ^{1}H NMR integration of the methyl resonance of the ester. The two diastereomers were inseparable using silica gel flash chromatography; the data is reported as a mixture of diastereomers, and * denotes the minor diastereomer.

4-Butyl-2-trifluoromethyloxepane-2-carboxylic acid methyl ester (16{*1*}). According to the general procedure for palladium catalyzed hydrogenation, **16**{*1*} was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.08 (td, 1 H, J = 13.2, 3.9 Hz), *3.85 (s, 1 H), 3.83 (s, 2 H), 3.63–3.55 (m, 1 H), 2.38 (d, 1 H, J = 13.2 Hz), 1.94–1.61 (m, 4 H), 1.29 (b s, 6 H), 0.90 (b s, 5 H).

General Procedure for Carbocyclization of 13{*1–2*}. An oven-dried 100 mL flask fitted with a stir bar was charged with methyl 2-(but-2-ynyloxy)-2-(trifluoromethyl)-6-methylhepta-3,4-dienoate **13**{*1*} (2.4 g, 8.3 mmol) and freshly distilled toluene (30 mL). The solution was degassed by bubbling argon through the solution for 2 min, then a rhodium biscarbonyl chloride dimer (0.16 g, 0.41 mmol) was added. After 5 min, the reaction was complete by thin-layer chromatography (TLC). The solution was passed through a plug of silica gel eluting with 6:1 hexane/EtOAc. Following removal of solvent under reduced pressure, the residue was then purified via silica gel flash chromatography to give **17**{*1*} (2.2 g, 93%).

(5*Z*)-Methyl 5-Ethylidene-2-(trifluoromethyl)-5,6-dihydro-4-(2-methylprop-1-enyl)-2*H*-pyran-2-carboxylate (17{*1*}). According to the general procedure for carbocyclization, **12**{*1*} was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.74 (q, 1 H, J = 7.0 Hz), 5.67 (s, 1 H), 5.59 (s, 1 H), 4.74 (d, 1 H, J = 13.7 Hz), 4.44 (d, 1 H, J = 13.7 Hz), 3.84 (s, 3 H), 2.04 (s, 3 H), 1.71 (d, 3 H, J = 7.0 Hz) 1.70 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.0, 139.2, 139.0, 129.4, 124.3, 122.9 (q, J = 284.0 Hz), 120.7, 115.0, 79.0 (q, J = 30.0 Hz), 62.2, 53.3, 25.9, 19.14, 13.19; IR (film) 2916, 1758, 1300 cm^{-1}.

General Procedure for Amide Formation from 15{*1*−*2,4*} or 16{*1–2,4–6*} with 18{*1–13*}. A 5 mL microwave vial equipped with acids (1 equiv) in CH_2Cl_2 was charged with PS-DCC (loading 1.20 mmol/g, 2 equiv) and 1-hydroxybenzotriazole (1.5 equiv). The reaction mixture was stirred at rt for 5 min before the addition of the amine. Volatile amines such as methyl amine **18**{*1*} (33 wt % in ethanol) and cyclopropanemethylamine **18**{*2*} were used in large excess (25 equiv). 2-Methyoxyethylamine **18**{*3*}, 4-(2-aminoethyl)morpholine **18**{*5*}, *N*-(2-hydroxyethyl)ethylenediamine **18**{*7*}, benzylamine **18**{*8*}, 4-methylsulfonyl-benzylamine hydrochloride **18**{*9*}, 2-aminomethyl pyridine **18**{*11*}, 5-methylfurylamine **18**{*12*}, and (1,5-dimethyl-1*H*-pyrazol)-methylamine **18**{*13*} were used in excess (2 equiv). In the case of **18**{*9*}, Et_3N (4 equiv) was added to neutralize the HCl salt. After addition of the amines, the microwave vials were sealed and irradiated for 10 min at 100 °C. Reactions involving volatile amines **18**{*1*} and **18**{*2*} were irradiated for 40 min at 60 °C. After cooling to rt, the crude mixture was loaded onto SPE-cartridges (prepacked with 500 mg silica-bound carbonate and preconditioned with CH_2Cl_2). The SPE cartridges were washed three times with CH_2Cl_2. The eluents were collected via gravity filtration and concentrated in a centrifugal vacuum evaporator (Genevac HT-4). The crude product was purified by automated ISCO (Optix 10) flash chromatography using hexane and EtOAc as eluents.

4-Butylidene-2-trifluoromethyloxepane-2-carboxylic acid benzylamide (*Z*-19{*1,8*}). According to the general procedure for amide formation, *Z*-**19**{*1,8*} was obtained as colorless crystals. Mp 63–65 °C; ^{1}H NMR ($CDCl_3$) δ 7.37–7.24 (m, 5 H), 5.41 (t, 1 H, J = 6.9 Hz), 4.55 (dd, 1 H, J = 15.0, 6.3 Hz), 4.36 (dd, 1 H, J = 15.0, 5.4 Hz), 4.09–4.06 (m, 2 H), 3.53 (d, 1 H, J = 14.4 Hz), 2.47 (d, 1 H, J = 14.4 Hz), 2.36 (td, 1 H, J = 13.5, 3.6 Hz), 2.14–2.01 (m, 2 H), 1.90–1.77 (m, 2 H), 1.66–1.49 (m, 2 H), 1.34–1.21 (m, 2 H), 0.89 (t, 3 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 167.1, 137.9, 132.6, 130.9, 128.9, 127.7, 124.9 (q, J_{CF} = 288.0 Hz), 82.1 (q, J_{CF} = 24.8 Hz), 67.8, 43.5, 39.7, 31.7, 31.4, 30.0, 23.1, 13.9; ^{19}F NMR ($CDCl_3$) δ −77.5 (s, 3 F); IR (film) 3307, 2961, 2916, 1684, 1672 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 355 (20), 312 (19), 123 (9), 106 (7), 91 (100), 81 (12); HRMS (EI) *m*/*z* calcd for $C_{18}H_{24}F_3NO_2$ 355.1759, found 355.1749.

4-Butyl-2-trifluoromethyloxepane-2-carboxylic acid benzylamide (major diastereomer of 20{*1,8*}). According to the general procedure for amide formation, **20**{*1,8*} was obtained as colorless crystals. Mp 84–88 °C; ^{1}H NMR ($CDCl_3$) δ 7.39–7.26 (m, 5 H), 7.07 (b s, 1 H), 4.56–4.43 (m, 2 H), 3.96 (d, 1 H, J = 13.5 Hz), 3.62–3.54 (m, 1 H), 2.48 (d, 1 H, J = 16.2 Hz), 2.06 (ddd, 1 H, J = 13.7, 11.7, 1.5 Hz), 1.90–1.81 (m, 1 H), 1.76–1.69 (m, 2 H), 1.30–1.06 (m, 8 H), 0.90 (t, 3 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 168.6, 137.8, 129.0, 127.9, 127.8, 124.3 (q, J_{CF} = 285.0 Hz), 83.2 (q, J_{CF} = 26.3 Hz), 68.1, 43.9, 36.5, 36.4, 36.2, 34.5, 30.0, 29.4, 23.0, 14.2; ^{19}F NMR ($CDCl_3$) δ −76.6 (s, 3 F); IR (film) 3429, 3339, 2930, 2855, 1674, 1518, 1455, 1261 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 357 (45), 223 (42), 204 (60), 163 (27), 111 (42), 91 (100); HRMS (EI) *m*/*z* calcd for $C_{18}H_{26}F_3NO_2$ 357.1916, found 357.1911.

General Procedure for NaCN-Catalyzed Amide Formation from 17{*1–2*} with 18{*1–13*}. An oven-dried microwave reactor vial equipped with a stir bar was charged with (5*Z*)-methyl 4-(cyclohexylidenemethyl)-5-ethylidene-2-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2- carboxylate **17**{*2*} (58 mg, 0.18 mmol), followed by sodium cyanide (1.7 mg, 0.035 mmol). To the tube was then added methylamine **18**{*1*} (0.66 mL, 33% solution in methanol, 5.3 mmol). The tube was capped and heated in the microwave using a temperature of 100 °C, ramp time of 5 min, hold time of 120 min, and a maximum power of 300 W. Following the reaction, the mixture was poured into CH_2Cl_2 (10 mL) and washed with water (1 × 10 mL) to remove sodium cyanide. The organic solution was then diluted with CH_2Cl_2 (10 mL), washed with 1 M HCl (3 × 10 mL), water (1 × 10 mL), and then brine (1 × 10 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography to give **21**{*2,1*} (10 mg, 17%).

(5*Z*)-4-(Cyclohexylidenemethyl)-5-ethylidene-2-(trifluoromethyl)-5,6-dihydro-*N*-methyl-2*H*-pyran-2-carboxamide (21{*2,1*}). According to the general procedure for NaCN-catalyzed amide formation, **21**{*2,1*} was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.83 (b s, 1 H), 5.82–5.76 (m, 2 H), 5.60 (s, 1 H), 4.63 (d, 1 H, J = 13.3 Hz), 4.54 (d, 1 H, J = 13.3 Hz), 2.85 (d, 3 H, J = 5.0 Hz), 2.18–2.13 (m, 4 H), 1.72 (d, 3 H, J = 7.2 Hz), 1.57–1.44 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 146.7, 137.6, 129.3, 124.0, 123.6 (q, J = 287.0 Hz), 117.4, 115.9, 78.0 (q, J = 30.0 Hz), 62.5, 37.2, 29.8, 28.6, 28.0, 26.6, 26.1, 13.2; IR (film) 3338, 2930, 1679, 1524 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 681 ([2 M + Na]$^+$, 12), 579 (100), 352 ([M + Na]$^+$, 35), 301 (85), 225 (45).

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Note Added after ASAP Publication. There was an error in Table 3 in the version published ASAP February 14, 2008; the corrected version published ASAP February 16, 2008.

Supporting Information Available. Experimental procedures and spectroscopic data for compounds **11**{*2*}, **11**{*3*}, **11**{*4*}, **11**{*5*}, **11**{*6*}, **11**{*8*}, **20**{*1,8*}, **20**{*2,8*}, **20**{*5,8*}, **20**{*2,12*}, *Z*-**19**{*2,8*}, *Z*-**19**{*2,2*}, *Z*-**19**{*4,1*}, *E*-**19**{*4,1*}, **20**{*4,8*}, **20**{*4,11*}, and **20**{*6,11*}, the experimental details of diversity analysis, and a crystallographic information file. This material is available free of charge via the Internet at http://pubs.acs.org.

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