HETEROCYCLES, Vol. 70, 2006, pp. 367 - 388. © The Japan Institute of Heterocyclic Chemistry
Received, 1st September, 2006, Accepted, 17th November, 2006, Published online, 21st November, 2006. COM-06-S(W)36

CYCLOADDITION REACTIONS OF AMINO-ACID DERIVED CROSS-CONJUGATED TRIENES: STEREOSELECTIVE SYNTHESIS OF NOVEL HETEROCYCLIC SCAFFOLDS

Branko Mitasev, Bingli Yan, and Kay M. Brummond*

University of Pittsburgh, Department of Chemistry, Pittsburgh, PA 15260, USA. Email: kbrummon@pitt.edu

Abstract – Cross-conjugated trienes obtained via a Rh(I)-catalyzed allenic Alder-ene reaction represent a new class of compounds. The synthesis of heterocyclic compounds containing multiple fused rings was accomplished via sequential Diels-Alder reactions of amino-acid derived cross-conjugated trienes. Newly synthesized imino-oxazolidinone fused trienes were used to control the stereoselectivity in an intermolecular cycloaddition sequence. Additionally, intramolecular cycloaddition of ester tethered tetraene stereoselectively afforded fused tricyclic pyridino-pyranone which was effectively utilized in subsequent cycloaddition reactions.

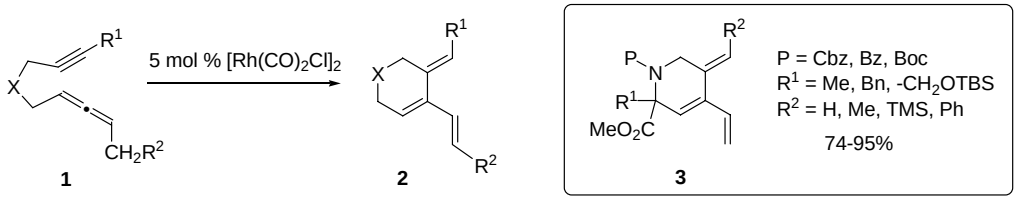
INTRODUCTION

The discovery of novel transition metal catalyzed cycloisomerization and cycloaddition reactions is an intense area of research.[1] Sometimes, these new methods allow the synthetic chemist to effect transformations that may normally require forcing thermal conditions. Examples include Rh(I)-catalyzed [2+2+1],[2] [5+2] and [4+2] cycloaddition reactions,[3, 4] and ene-type cycloisomerizations.[5] Our group is actively involved in studying transition metal catalyzed reactions of allenes. We reported that Rh(I)-catalyzed allenic Alder-ene reaction of 1,5-allenynes (**1**) affords cross-conjugated trienes (**2**) (Scheme 1).[6] The scope of this transformation was subsequently extended, allowing access to amino-ester tethered trienes (**3**).[7] The resulting trienes can be used in a variety of ways, including tandem transition metal catalyzed carbon-carbon bond forming reactions to provide compounds of high molecular complexity in one pot.[8] Herein, we report our approach to diversification of the amino-ester tethered trienes (**3**) via sequential Diels-Alder reactions, hoping this strategy can be extended to other cycloadditions (e.g. [4+3], [4+4]). Applying cycloaddition reactions of amino-ester tethered trienes (**3**) to

---

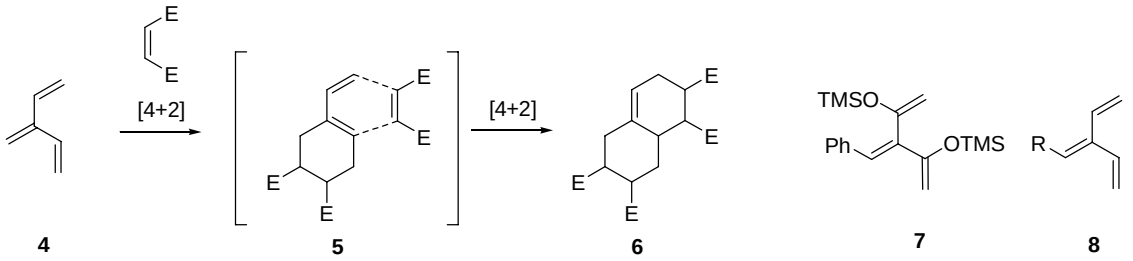
This paper is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

diversity-oriented synthesis is appealing because the products may serve as useful biological probes.[9, 10] Sequential Diels-Alder reactions of these trienes can quickly lead to complex molecular scaffolds, particularly if two different dienophiles are utilized.



Scheme 1. Cyclic cross-conjugated trienes via a Rh(I)-catalyzed Alder-ene reaction.

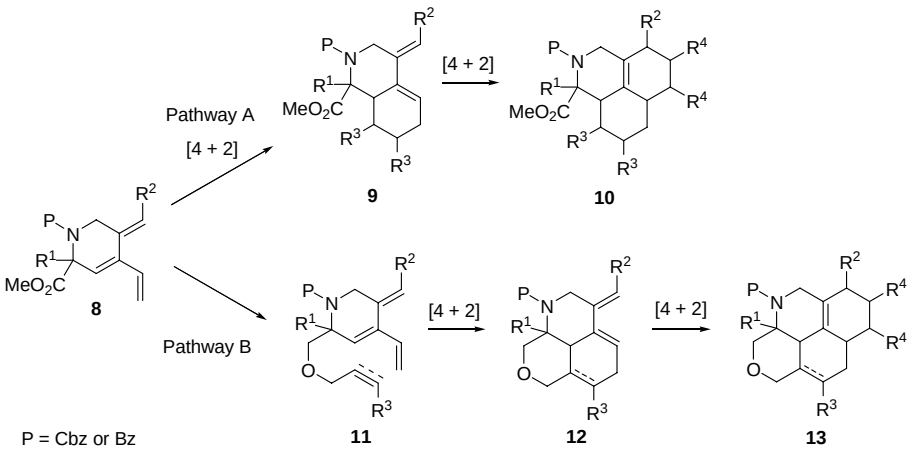
Sequential Diels-Alder reactions of acyclic cross-conjugated trienes (**4**) affording functionalized decalins (**6**) were initially studied by Tsuge,[11] who utilized bis-silylenolether (**7**), and Fallis, employing monosubstituted triene (**8**) (Scheme 2).[12] Acyclic cross-conjugated tetraene ([4]dendralene) was also recently examined for participation in tandem Diels-Alder reactions by Willis and coworkers.[13] However, sequential reactions of these acyclic trienes and tetraenes have proven difficult to control, typically affording mixtures of regioisomers. Moreover, preparation of the acyclic polyenes is not trivial, in part due to their instability. Therefore, these compounds have seen only limited synthetic application, despite their potential.[14] The cyclic trienes obtained via an allenic Alder-ene reaction (Scheme 1) offer a solution to the regioselectivity issue by locking one of the dienes in an unreactive *s-trans* conformation.



Scheme 2. Tandem Diels-Alder reactions of acyclic cross-conjugated trienes.

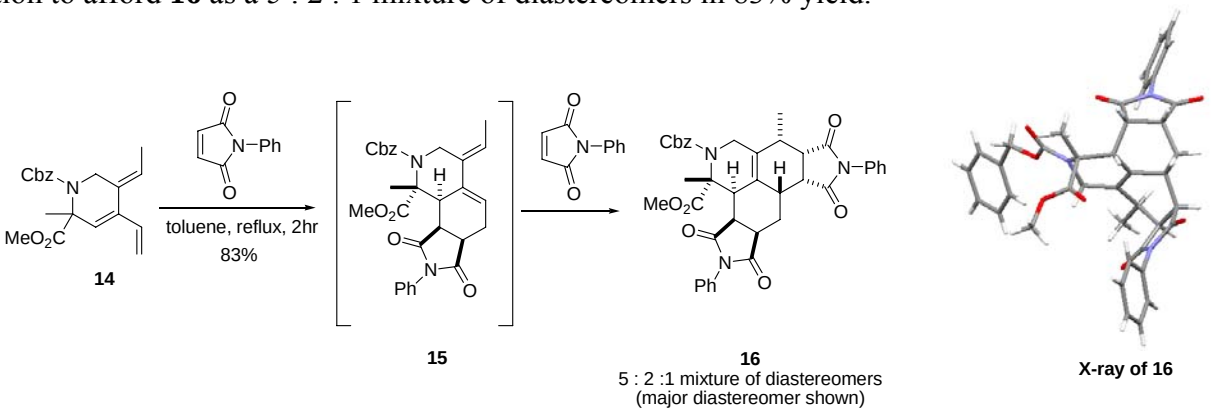
RESULTS AND DISCUSSION

We were interested in exploring the feasibility of both cycloaddition pathways illustrated in Scheme 3. Pathway A involves sequential intermolecular cycloaddition reactions of triene (**8)** using two different dienophiles (**8→9→10**). Alternatively, pathway B, involves an intra-/intermolecular cycloaddition sequence (**8→11→12→13)**.



Scheme 3. Diels-Alder reactions of triene (**8**).

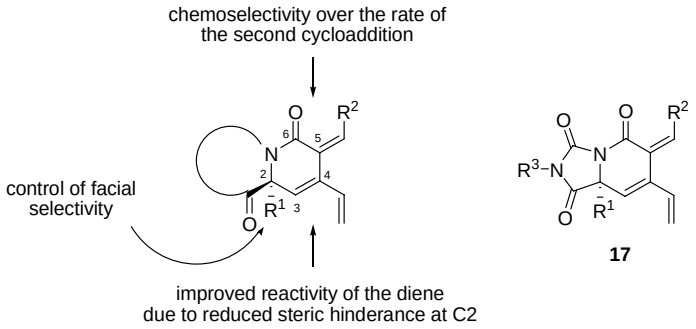
First Generation Triene. The more direct pathway A was initially more appealing, so our investigations began with the reaction of triene (**14**) with *N*-phenylmaleimide (Scheme 4). Unfortunately, the initial Diels-Alder cycloadduct (**15**) was not observed, but it immediately underwent a second Diels-Alder reaction to afford **16** as a 5 : 2 : 1 mixture of diastereomers in 83% yield.



Scheme 4. Intermolecular Diels-Alder reaction of **14** with *N*-phenylmaleimide.

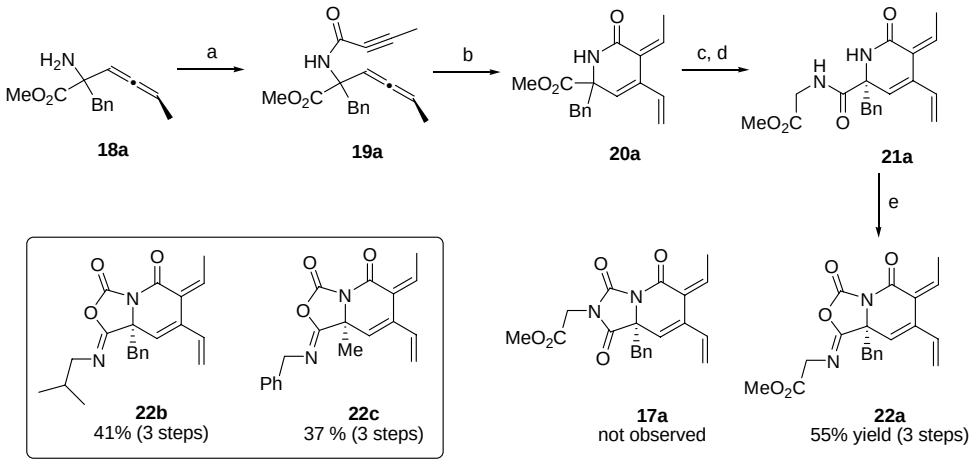
The relative stereochemistry of the major diastereomer was assigned by X-ray crystallography, and results from *endo* selectivity in the first cycloaddition occuring from the same face of the methyl group, and the second dienophile adding from the less hindered convex face of the newly formed diene in *endo* mode. Attempts to obtain the cycloadduct (**15**), by reaction of **14** with equimolar amount of dienophile resulted in formation of **16** and recovered triene. This result is attributed to the higher reactivity of the second diene of **15** because it is locked in an *s-cis* conformation. Other dienophiles (maleic anhydride and 4-phenyl-[1,2,4]-triazole-3,5-dione) also reacted with **14** to give mixtures of diastereomeric products similar to **16**. Controlling the chemo- and diastereoselectivity of the Diels-Alder reaction of triene was important, so a new strategy for tandem intermolecular cycloaddition was considered. It was reasoned that tying back the appending ester in a ring would increase the reactivity of the diene in the first

Diels-Alder reaction by reducing the steric bulk. Moreover, this constraint leads to a sterically biased triene, in which one face is blocked by the R^1 group. Finally, introducing an electron withdrawing carbonyl group at the C6 position would slow the second Diels-Alder reaction. The novel imidazo-pyridinone triene (**17**) addresses all of these issues (Scheme 5).



Scheme 5. Novel fused bicyclic Diels-Alder precursor (**17**).

Second Generation Triene. Introduction of the carbonyl group at the C6 position has been previously put into practice by demonstrating the conversion of substituted propiolamides to unsaturated δ-lactam trienes via a Rh(I) catalyzed allenic Alder-ene reaction.[15] For example, conversion of the amine (**18a**) to butynamide (**19a**) was accomplished in 85% yield by coupling with 2-butynoic acid using *i*-butylchloroformate and *N*-methylmorpholine. Next, **19a** was subjected to $[Rh(CO)_2Cl]_2$ affording a 92% yield of δ-lactam triene (**20a**).[15]



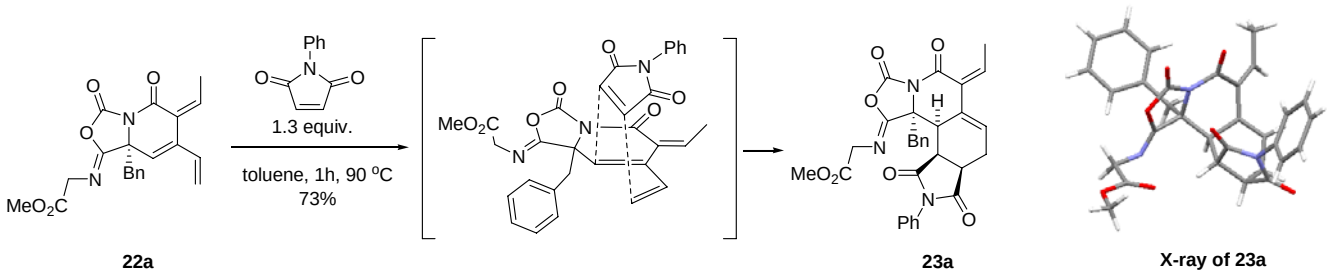
Conditions: (a)i-BuOCOCl, NMM, $CH_3CCCOOH$ then **18a**, 85%; (b) 10 mol % $[Rh(CO)_2Cl]_2$, toluene, 90 °C, 92%; (c) LiOH, THF / H_2O; (d) $MeO_2CCH_2NH_2$, HOBt, DMAP, EDCI; (e) phosgene (20% in toluene), Et_3N, CH_2Cl_2.

Scheme 6. Synthesis of imino-oxazolidinone precursors.

Tying back the ester moiety was accomplished by saponification of the methyl ester of **20a** using LiOH, followed by coupling of the resulting acid with glycine-methyl ester to give diamide (**21a**) (Scheme 6). Diamide (**21a**) was reacted with phosgene, to afford the unexpected imino-oxazolidinone (**22a**) in 55% yield (3 steps) and none of hydantoin (**17a**).[16] Nevertheless, **22a** should provide the same steric and

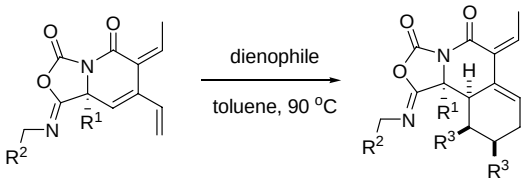
electronic control elements as hydantoin (**17a**). Two additional substrates, (**22b** and **22c**) were prepared using the same protocol in 41% and 37% yield over three steps, respectively.[17] To our knowledge, oxazolidinones with this substitution pattern have not been reported.[18]

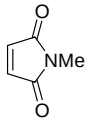
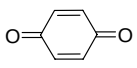
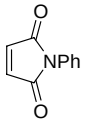
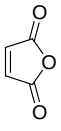
Triene (**22a**) was then tested in an intermolecular Diels-Alder reaction with *N*-phenylmaleimide (1.3 equiv.). The Diels-Alder cycloaddition occurred in less than 1 h at 90 °C to afford the cycloadduct (**23a**) in 73% yield as a single diastereomer (Scheme 7). The relative stereochemistry of **23a** was assigned by X-ray crystallography confirming that the cycloaddition occurred with *endo* selectivity and the diene approached from the opposite face of the benzyl group. Excess dienophile (2 equiv) still gave exclusive formation of **23a**, indicating a reduction in the rate of the second cycloaddition.



Scheme 7. Diels-Alder reaction of triene (**22a**).

Table 1. Diels-Alder reactions of trienes (**22b** and **22c**).



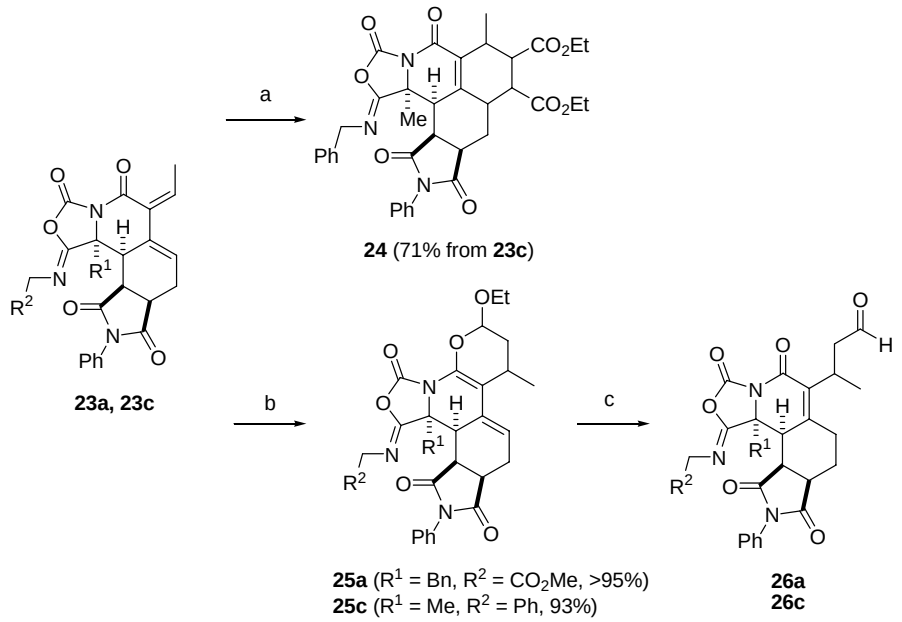
Entry / Precursor	Dienophile	Product	Time	Yield*	Entry / Precursor	Dienophile	Product	Time	Yield*
1 / **22b**		**23b**	2 h	95%	4 / **22c**		**23e**	5 h	23%
2 / **22c**		**23c**	1 h	73%	5 / **22c**		**23f**	7 h	24%
3 / **22c**		**23d**	15 h	41%	6 / **22c**		NR	-	-

* Reactions were run until all starting material was consumed. No byproducts were isolated.

Trienes (**22b** and **22c**) were also tested in Diels-Alder reactions (Table 1). Reaction of **22b** (R^1 = Bn) with *N*-methylmaleimide (NMM) resulted in 95% yield of cycloadduct (**23b**) as a single diastereomer (entry 1). Similarly, **22c** (R^1 = Me) reacted with *N*-phenylmaleimide to give **23c** in 73% yield. Other dienophiles were problematic. For example, reaction of **22c** with diethyl fumarate, *p*-benzoquinone and

dimethylacetylene dicarboxylate (DMAD) resulted in low to moderate yields of the desired products (entries 3, 4 and 5 respectively).[19] Finally, reaction of **22c** with maleic anhydride did not proceed (entry 6).[20]

We next examined the subsequent Diels-Alder reaction of **23a** and **23c**. As expected, these electronically and sterically deactivated dienes exhibited very low reactivity towards dienophiles. Reaction of **23c** with diethyl fumarate occurred at 90 °C to give **24** in 71% yield as an 8 : 1 mixture of diastereomers (Scheme 8). However, the same transformation of **23a** afforded the product in 59% yield as a 1 : 1 mixture of diastereomers (not shown).



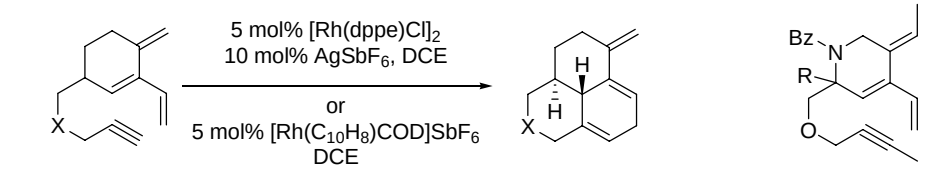
Conditions: (a) diethyl fumarate, toluene, 90 °C; (b) ethyl vinyl ether, dichloroethane, 10 mol % $Eu(fod)_3$, rt to 50 °C; (c) 1M HCl, $CDCl_3$, rt.

Scheme 8. Diels-Alder reactions of dienes (**23a** and **23c**).

Next, the thermal reaction of the electron deficient diene of **23a** with ethyl vinyl ether at 90 °C was attempted, affording 70% yield of the pyran (**25a**). This was somewhat unexpected since only a few hetero-Diels-Alder reactions of α,β-unsaturated amides have been reported, and generally result in formation of an aromatic compound (*e.g.* indole,[21a] thiazole,[21b] pyrazole,[21c]). Alternatively, $Eu(fod)_3$ catalyzed the same transformation at room temperature, giving **25a** in 95% yield as a single diastereomer (Scheme 8).[22] Reaction of **23c** under the $Eu(fod)_3$-catalyzed conditions produced **25c** in 93% yield. Exposure of **25a** and **25c** to aqueous HCl afforded the aldehydes (**26a** and **26c**), respectively, resulting from hydrolysis of the acetal moiety and isomerization of the double bond into conjugation with the amide.

Thus, by sterically and electronically modifying triene (**14**) to amide (**22**), we were able to control the diastereo- and chemoselectivity of the subsequent cycloaddition reactions. The level of control that was achieved will be very useful in the preparation of a discovery library.

Pathway B in Scheme 3, the intra-/intermolecular cycloaddition sequence was examined next. We have previously shown that triene-yne systems (**27**), undergo a Rh(I) catalyzed formal [4+2] cycloaddition to afford tricyclic trienes (**28**) (Scheme 9).[8] We were interested in applying this same strategy to the amino-acid derived substrates. Triene-yne (**29**) was synthesized and subjected to our previously reported conditions ($[Rh(dppe)Cl]_2$, $AgSbF_6$, 1,2-dichloroethane)[8, 23] which resulted in recovered starting material. Other reaction conditions known to catalyze the formal [4+2] reaction of diene-ynes did not effect the desired cycloaddition either.[24, 4]

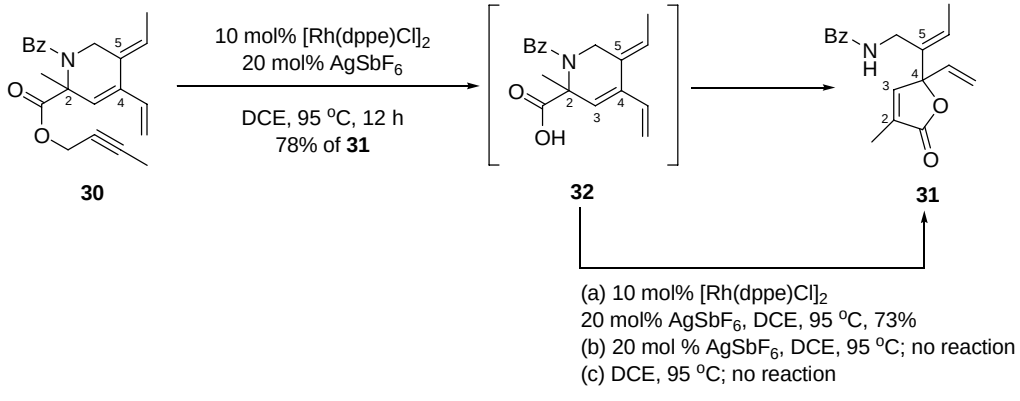


27 **28** **29**

X = O, NTs, $C(CO_2Et)_2$ R = Bn, Me

Scheme 9. Rh(I)-catalyzed [4+2] cycloaddition of cross-conjugated trienes.

Interestingly, prolonged heating of butynyl-ester (**30**) in presence of *in situ* generated catalytic Rh(I) ($[Rh(dppe)Cl]_2$, $AgSbF_6$, 1,2-dichloroethane) resulted in formation of γ-butenolide (**31**) in 78% yield (Scheme 10). Compound (**31**) was rationalized to arise from Rh(I)-catalyzed depropargylation of **30**, followed by cyclization of the resulting acid of **32** onto C4, concomitant with allylic disposition of the C2 benzamide. This hypothesis was supported by independently synthesizing acid (**32)** and subjecting it to the same reaction conditions which resulted in 73% yield of **31**. Heating **32** in presence of 20 mol% $AgSbF_6$ alone gave no reaction, indicating that the cyclization is not catalyzed by the silver salt additive.[25] Furthermore, heating **32** in 1,2-dichloroethane also gave recovered starting material. Additional experiments are underway to gain insight into the mechanism of this transformation which represents an overall 5-*endo-trig* process known to be disfavored by Baldwin's guidelines.[26] The Rh(I)-catalyzed substitution of activated allylic amines finds precedent in recent work by Lautens.[27]

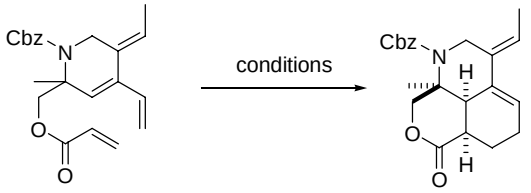


30 **32** **31**

Scheme 10. Unexpected formation of γ-butenolide (**31**).

We finally turned our attention to examining a thermal intramolecular Diels-Alder reaction. For this purpose, tetraene (**33**) (Table 2) was synthesized by reduction of the methyl ester of **14** using DIBALH, followed by condensation of the resulting alcohol with acryloyl chloride (see experimental section). The reactive portion of this cycloaddition precursor, a hexadienyl-acrylate, belongs to a class of substrates whose application in synthesis remains underutilized.[28] Promoting the desired cycloaddition by heating **33** in toluene at 110 °C resulted in decomposition over 24 h period (Table 2, entry 1). Attempts to catalyze this reaction with Et_2AlCl or $BF_3{\cdot}OEt_2$ gave either no reaction or decomposition, depending on the temperature (see entries 2, 3 and 4).[29, 30]

Table 2. Conditions for Diels-Alder reaction of **33**.



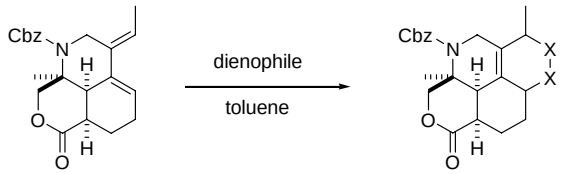
33 **34**

Entry	Conditions	Result / Yield%
1	toluene, 110 ^oC	decomposition
2	Et_2AlCl, toluene, -78 ^oC	no reaction
3	Et_2AlCl, toluene, 80 ^oC	decomposition
4	BF_3OEt_2, toluene, 80 ^oC	decomposition
5	acetonitrile, 90 ^oC	no reaction
6	DMSO, 80 ^oC, 8h	43%
7	DMSO / H_2O, 80 ^oC, 6h	50%

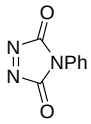
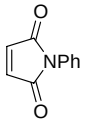
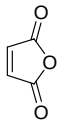
Next, more polar solvents were examined, and the reaction was found to proceed in DMSO, at 80 °C, giving 43% yield of the desired tricyclic lactone (**34**) as a single diastereomer. The relative stereochemistry, resulting from *endo* cycloaddition, was assigned based on the X-ray crystal structure of a later intermediate (**35b**) (Table 3, *vide infra*). The cycloaddition could be marginally accelerated by using a mixed solvent system consisting of DMSO / H_2O (2 : 1).[31] With **34** in hand, we examined its participation in subsequent intermolecular Diels-Alder reactions (Table 3). Reaction with 4-phenyl[1,2,4]triazole-3,5-dione was complete in 5 min to afford **35a** as a single diastereomer (entry 1). *N*-Phenylmaleimide reacted at rt within 6 h to give **35b** in 95% yield and diastereoselectivity greater than 10 : 1 (entry 2). The relative stereochemistry of **35b** was established by X-ray crystallography indicating *endo* approach of the dienophile from the convex face of the fused tricycle. Maleic anhydride reacted similarly to give **35c** (entry 3). Dimethylacetylene dicarboxylate (DMAD) reacted slower and produced **35d** as a 4 : 1 mixture of diastereomers after 10 h at 35 °C (entry 4). It should be noted that compounds (**35a-c**) possess a steroidal-like heterocyclic skeleton, and may therefore serve as useful biological probes. The rapid manner and selectivity by which these scaffolds can be assembled using this strategy make it attractive for generation of libraries of compounds.

In conclusion, we have demonstrated the use of amino-ester tethered cross-conjugated trienes in rapid generation of molecular complexity with Diels-Alder reactions. Several unique heterocyclic scaffolds were accessed using different strategies. Novel imino-oxazolidinone fused trienes (**22a-c**) were synthesized, and used to control the reactivity and steroselectivity in the intermolecular cycloaddition reactions. Furthermore, the intramolecular cycloaddition of an appended acrylate moiety proceeded in polar solvents to give tricyclic lactone (**34**). The newly generated diene in this compound exhibited reactivity towards a set of active dienophiles, affording highly functionalized tetra- and pentacyclic skeletons in stereoselective fashion. Overall, the routes developed here are applicable to the synthesis of libraries of compounds via parallel solution phase methods. That work is underway at the University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD) and will be reported in due course.

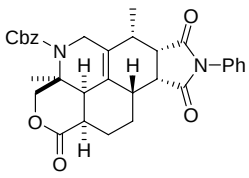
Table 3. Diels-Alder reactions of tricyclic diene (**34**).



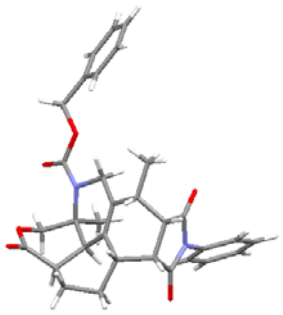
34 **35a-d**

Entry / Product	Dienophile	Temperature / Time	Yield	dr[a]
1 / **35a**[b]		rt / 5 min	95%	1 : 0
2 / **35b**[c]		rt / 6 h	95%	> 10 : 1
3 / **35c**[c]		rt / 3 h	78%	> 10 : 1
4 / **35d**[d]	MeO_2C—≡—CO_2Me	35 °C / 10 h	94%	4 : 1

Notes: [a] diastereomer ratio; [b] 1 equiv. of dienophile was used; [c] 1.5 equiv. of dienophile was used; [d] 6 equiv. of dienophile was used.



35b



X-ray of 35b

EXPERIMENTAL

All commercial reagents were used without further purification unless otherwise noted. All reactions were carried out under nitrogen atmosphere. Toluene, 1,2-dichloroethane and triethylamine (Et_3N) were all freshly distilled from CaH_2 prior to use. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purified over alumina using the SolTek ST-002 solvent purification system. Purification of the compounds by flash chromatography was performed by using silica gel (32-63 μm particle size, 60 Å

pore size). HPLC purification was performed on a Varian-Prostar 210 instrument using a Varian Microsorb Dynamax 100-5 Si column (5 μm packing, 250 mm x 10 mm). All ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 300 or 500 MHz instrument at room temperature, and chemical shifts (δ) reported relative to residual solvent peak $CHCl_3$ (7.27 ppm and 77.0 ppm respectively). High-resolution mass spectra (HRMS) were obtained on a Micromass Autospec and are reported as *m/z* (relative intensity). Accurate masses are reported for the molecular ion $[M]^+$ or a suitable fragment ion. CIF files for **16** (CCDC 618793), **23a** (CCDC 618794), **35b** (CCDC 618795) were deposited at the Cambridge Crystallographic Data Centre (CCDC) and are available free of charge (http://www.ccdc.cam.ac.uk/). Stick model representations of the X-ray structures used in the text were generated using Mercury v.1.4.1. (http://www.ccdc.cam.ac.uk/mercury/).

Diels-Alder cycloadduct (16). To a solution of triene (**14**)[15] (0.018 g, 0.053 mmol), in toluene (1 mL), was added *N*-phenylmaleimide (0.031 g, 0.23 mmol). The reaction was heated to reflux for 2 h. The solution was then cooled to rt, and directly applied to a silica gel column and purified by flash chromatography (hexanes-EtOAc, 1 : 4, v/v then EtOAc) to afford **16** (0.030 g, 83%). Further purification of the major diastereomer was performed using HPLC (hexanes-EtOAc, 3 : 2, v/v). **16** (major diastereomer, eluting first). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.13 (m, 5 H), 7.31-7.22 (m, 5H), 7.20-7.16 (m, 3H), 7.04 (d, *J* = 7.2 Hz, 2H), 5.11 (d, *J* = 12.7 Hz, 1H), 5.01 (d, *J* = 12.7 Hz, 1H), 4.46 (d, *J* = 18.9 Hz, 1H), 3.54-2.51 (m, 2H), 3.42-3.39 (m, 1H), 3.36 (s, 3H), 3.29 (bs, 1H), 3.15 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.03 (dd, *J* = 8.8, 5.6 Hz, 1H), 2.65 (dd, *J* = 13.9, 5.3 Hz, 1H), 2.51-2.47 (m, 1H), 2.45 (bs, 1H), 2.25 (bs, 1H), 2.06 (s, 3H), 1.42 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 176.2, 175.4, 175.2, 174.3, 156.2, 136.8, 133.4, 131.8, 131.6, 129.1, 128.7, 128.6, 128.3, 127.6, 127.4, 126.7, 126.2, 67.0, 63.7, 53.0, 45.7, 44.3, 43.3, 40.8, 40.4, 39.9, 33.5, 32.7, 24.5, 23.2, 12.7; IR (thin film) ν 2945, 1708, 1499, 1383 cm^{-1}; EI-HRMS calcd for $C_{40}H_{38}N_3O_8$ *m/z* $[M+1]^+$ 688.2659; found 688.2637.

Preparation of diamide (21a) (General procedure A). To a solution of **20a**[15] (0.916 g, 3.08 mmol) in THF (60 mL) was added water (60 mL) at rt, followed by $LiOH{\cdot}H_2O$ (0.264 g, 6.15 mmol). The homogeneous solution was stirred for 5 min, and then acidified with sat'd aq. NH_4Cl (200 mL) and 1M HCl (20 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the extracts were combined, dried over $MgSO_4$ and concentrated under vacuum to afford the desired carboxylic acid, which was then dissolved in CH_2Cl_2 (70 mL). To this solution were then added, 1-hydroxybenzotriazole (0.407 g 3.10 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide·HCl (0.579 g, 3.10 mmol), 4-dimethylaminopyridine (0.738 g, 6.20 mmol) and gycine methylester·HCl (0.379 g, 3.10 mmol) at rt. The reaction was stirred at rt for 90 min, and then diluted with CH_2Cl_2 (150 mL). The solution was washed with water (50 mL), sat'd aq. NH_4Cl (2 x 50 mL), then dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by flash chromatography (hexanes-EtOAc,

4 : 1 to 1 : 1, v/v) afforded **21a** (0.710 g, 65%) which was used in the next step without purification.

21a : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.35 (m, 1H), 7.28-7.15 (m, 5H), 6.96 (bs, 1H), 6.27 (dd, *J* = 17.1, 10.7 Hz, 1H), 6.14 (q, *J* = 7.5 Hz, 1H), 5.88 (s, 1H), 5.45 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.21 (dd, *J* = 10.8, 1.63 Hz, 1H), 4.16 (dd, *J* = 18.0, 5.9 Hz, 1H), 3.93 (dd, *J* = 18.0, 5.2 Hz, 1H), 3.72 (s, 3H), 3.41 (d, *J* = 13.4 Hz, 1H), 3.16 (d, *J* = 13.4 Hz, 1H), 2.12 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.2, 165.8, 138.9, 137.4, 134.5, 133.6, 130.8, 128.1, 127.1, 125.1, 120.9, 118.2, 65.8, 52.3, 44.9, 41.4, 16.0; IR (thin film) ν 3304, 2951, 1745, 1669, 1635, 1209 cm^{-1}; MS *m/z* (%) 354 (9), 263 (40), 238 (100), 174 (31), 91 (90); EI-HRMS calcd for $C_{20}H_{22}N_2O_4$ *m/z* $[M]^+$ 354.1580; found 354.1582.

21b : Prepared by following general procedure A, using **20a**[15] (0.240 g, 0.808 mmol), 1-hydroxybenzotriazole (0.109 g, 0.808 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (0.155 g, 0.808 mmol), 4-dimethylaminopyridine (0.098 g, 0.81 mmol) and *i*-butylamine (0.081 mL, 0.81 mmol). Isolated yield **21b** (0.178 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.15 (m, 5H), 6.55 (bs, 1H), 6.43-6.35 (m, 1H), 6.31 (ddd, *J* = 17.2, 10.8, 0.9 Hz, 1H), 6.24 (q, *J* = 7.5 Hz, 1H), 5.98 (s, 1H), 5.47 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dd, *J* = 10.8, 1.6 Hz, 1H), 3.53 (d, *J* = 13.2 Hz, 1H), 3.04-2.96 (m, 3H), 2.18 (d, *J* = 7.5 Hz, 3H), 1.70 (sep, *J* = 6.7 Hz, 1H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 165.7, 139.0, 136.6, 134.3, 133.6, 130.5, 128.4, 127.2, 125.2, 122.1, 118.2, 65.8, 47.2, 45.3, 28.2, 19.9, 16.1; IR (thin film) ν 3337, 2959, 1671, 1636 cm^{-1}; MS *m/z* (%) 338 (9), 247 (11), 238 (100), 91 (65).

21c : Prepared by following general procedure A, using **20c**[15] (0.101 g, 0.468 mmol), $LiOH·H_2O$ (0.038 g, 0.92 mmol), 1-hydroxybenzotriazole (0.065 g, 0.48 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide·HCl (0.093 g, 0.48 mmol), 4-dimethylaminopyridine (0.062 g, 0.51 mmol) and benzylamine (0.053 mL, 0.48 mmol). Isolated yield **21c** (0.109 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17-7.29 (m, 5H), 6.88 (bs, 1H), 6.78 (bs, 1H), 6.36 (q, *J* = 17.6, 10.6 Hz, 2H), 5.88 (s, 1H), 5.49 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.26 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.40 (d, *J* = 5.7 Hz, 2H), 2.23 (d, *J* = 7.4 Hz, 3H), 1.63 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 172.2, 165.8, 139.6, 137.9, 136.6, 133.8, 128.9, 127.7, 127.6, 125.4, 123.1, 118.7, 62.2, 43.9, 27.3, 16.3; IR (neat) 1672, 1634 cm^{-1}; EI-HRMS calcd for $C_{18}H_{20}N_2O_2$ $[M]^+$ *m/z* 296.1525, found 296.1528.

Preparation of imino-oxazolidinone (22a) (General procedure B). A solution of **21a** (0.710 g, 2.01 mmol) in CH_2Cl_2 (150 mL) was cooled to -10 ºC, and Et_3N (0.839 mL, 6.03 mmol) was added. Then, phosgene (1.42 mL, 3.02 mmol of a 20 % solution in toluene) was added dropwise, and the reaction was stirred for 10 min at -10 ºC. After quenching the reaction by adding water (10 mL), the organic layer was washed with diluted NH_4Cl solution (2 x 100 mL) to remove the excess Et_3N, dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purifed by flash chromatography (hexanes-EtOAc, 4 : 1 to 1 : 1, v/v) to afford the imino-oxazolidinone (**22a**) (0.645 g, 85%). Note: extended exposure of **22a** to

silica gel causes hydrolysis to **21a**.

22a : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.21 (m, 3H), 7.09-7.06 (m, 2H), 6.23 (s, 1H), 6.23 (q, *J* = 7.5 Hz, 1H), 6.19 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.56 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.32 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.25 (s, 2H), 3.81 (s, 3H), 3.22 (d, *J* = 13.6 Hz, 1H), 3.11 (d, *J* = 13.6 Hz, 1H), 2.04 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 160.4, 153.3, 146.0, 144.7, 138.8, 132.7, 132.1, 131.0, 128.5, 128.0, 126.8, 119.6, 118.9, 66.6, 52.3, 49.2, 47.5, 16.3; IR (thin film) ν 2953, 1840, 1744, 1272 cm^{-1}; MS *m/z* (%) 380 (32), 336 (14), 245 (61), 217 (35), 91 (100); EI-HRMS calcd for $C_{21}H_{20}N_2O_5$ *m/z* $[M]^+$ 380.1372; found 380.1370.

22b : Prepared by following general procedure B, using **21b** (0.170 g, 0.503 mmol), Et_3N (0.182 mL, 0.159 mmol) and phosgene (0.310 mL, 0.657 mmol of a 20 % solution in toluene). Isolated yield **22b** (0.125 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.20 (m, 3H), 7.05-7.03 (m, 2H), 6.22-6.12 (m, 3H), 5.54 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.29 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.23 (d, *J* = 6.8 Hz, 2H), 3.12 (d, *J* = 13.5 Hz, 1H), 3.03 (d, *J* = 13.5 Hz, 1H), 1.99 (d, *J* = 7.5 Hz, 3H), 1.90 (sep, *J* = 6.7 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 149.1, 146.9, 144.0, 138.5, 132.7, 132.2, 130.8, 128.2, 127.8, 126.8, 119.3, 119.2, 66.0, 55.3, 47.4, 29.2, 20.4, 16.2; IR (thin film) ν 2956, 1836, 1743, 1269 cm^{-1}; MS *m/z* (%) 364 (6), 320 (19), 229 (33), 173 (100), 91 (63); EI-HRMS calcd for $C_{22}H_{24}N_2O_3$ *m/z* $[M]^+$ 364.1787; found 364.1786.

22c : Prepared by following general procedure B, using **21c** (0.850 g, 2.87 mmol), Et_3N (3.20 mL, 22.9 mmol) and phosgene (5.60 mL, 11.4 mmol of a 20 % solution in toluene). Isolated yield **22c** (0.516 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 5H), 6.67 (q, *J* = 14.7, 7.1 Hz, 1H), 6.29 (ddd, *J* = 17.3, 10.8, 0.9 Hz, 1H), 6.21 (s, 1H), 5.55 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.33 (dd, *J* = 10.8, 1.1 Hz, 1H), 4.65 (s, 2H), 2.31 (d, *J* = 7.5 Hz, 3H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 151.3, 146.9, 145.7, 138.6, 137.1, 133.1, 128.8, 127.9, 127.5, 127.4, 122.5, 119.8, 62.9, 51.8, 29.0, 16.4; IR (neat) 1840, 1742 cm^{-1}; MS *m/z* (%) 323 (7), 322 (26), 263 (15), 209 (16), 187 (30), 160 (24), 91 (100), 77 (22); EI-HRMS calcd for $C_{19}H_{18}N_2O_3$ $[M]^+$ *m/z* 322.1317, found 322.1237.

Preparation of cycloadduct (23a) (General procedure C). A solution of triene (**22a**) (0.063 g, 0.17 mmol) and *N*-phenylmaleimide (0.037 g, 0.22 mmol) in toluene (4 mL) was heated to 90 ºC until the starting material was completely consumed as evidenced by TLC analysis. During this time, **23a** began precipitating as a white solid. The mixture was cooled to 0 ºC in a test tube and centrifuged for 15 min. The toluene was decanted away and the solid rinsed with hexanes and dried under vacuum to afford **23a** (0.067 g, 73%).

23a : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.29 (m, 6H), 7.09-7.00 (m, 4H), 6.65 (q, *J* = 7.3 Hz, 1H), 6.25-6.19 (m, 1H), 4.36 (d, *J* = 18.0 Hz, 1H), 4.34 (dd, *J* = 9.0, 5.2 Hz, 1H), 4.22 (d, *J* = 18.1 Hz, 1H), 3.78 (s, 3H), 3.46 (t, *J* = 7.9 Hz, 1H), 3.37 (d, *J* = 13.5 Hz, 1H), 3.27 (d, *J* = 13.5 Hz, 1H), 3.10 (bs, 1H),

3.09-3.02 (m, 1H), 2.31 (d, *J* = 7.4 Hz, 3H); 2.35-2.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 176.1, 170.1, 159.5, 153.6, 146.2, 141.3, 135.6, 132.2, 131.1, 130.0, 129.8, 129.0, 128.7, 128.4, 126.2, 126.0, 123.7, 66.2, 52.2, 48.9, 48.4, 41.6, 40.6, 39.6, 25.7, 16.0; IR (thin film) ν 1842, 1741, 1711, 1290 cm^{-1}; MS *m/z* (%) 553 (5), 509 (18), 462 (76), 418 (85), 319 (83), 91 (100); EI-HRMS calcd for $C_{31}H_{27}N_3O_7$ *m/z* $[M]^+$ 553.1849; found 553.1830.

23b : Prepared by following general procedure C, using **22b** (0.115 g, 0.276 mmol), *N*-methylmaleimide (0.040 g, 0.359 mmol). Precipitation of the product from the toluene solution was accomplished by addition of hexanes (2 mL) and refrigeration at -10 °C for 2 days under N_2. Isolated yield **23b** (0.133 g, >95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.27 (m, 3H), 6.98-6.95 (m, 2H), 6.58 (q, *J* = 7.4, 1H), 6.12-6.08 (m, 1H), 3.88 (dd, *J* = 8.9, 5.2 Hz, 1H), 3.36-3.20 (m, 5H), 3.16 (d, *J* = 13.4 Hz, 1H), 3.02-2.92 (m, 2H), 2.86 (d, *J* = 3.8 Hz, 1H), 2.83 (s, 3H), 2.28 (d, *J* = 7.4 Hz, 3H), 1.91 (sep, *J* = 6.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 176.5, 159.8, 149.7, 147.1, 140.7, 135.6, 132.5, 130.2, 129.8, 128.9, 128.2, 123.4, 65.8, 55.5, 48.6, 41.4, 40.7, 39.5, 29.3, 25.3, 25.1, 20.8, 20.7, 15.8; IR (thin film) ν 2955, 1835, 1740, 1699 cm^{-1}; MS *m/z* (%) 475 (15), 384 (77), 340 (100), 284 (80), 257 (63), 91 (58); EI-HRMS calcd for $C_{27}H_{29}N_3O_5$ *m/z* $[M]^+$ 475.2107; found 475.2107.

23c : Prepared by following general procedure C, using **22c** (0.134 g, 0.483 mmol), *N*-phenylmaleimide (0.094 g, 0.54 mmol). The toluene was removed under vacuum and the crude residue purified by flash chromatography to afford **23c** (0.150 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.57 (m, 8H), 7.17-7.23 (m, 2H), 6.71 (q, *J* = 14.8, 7.4 Hz, 1H), 6.29 (m, 1H), 4.89 (d, *J* = 14.6 Hz, 1H), 4.79 (d, *J* = 14.6 Hz, 1H), 4.05 (dd, *J* = 9.1, 5.3 Hz, 1H), 3.45 (t, *J* = 7.9 Hz, 1H), 3.14 (dd, *J* = 15.4, 7.6 Hz, 1H), 3.02 (m, 1H), 2.35 (d, *J* = 7.4 Hz, 3H), 2.31 (m, 1H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 176.1, 159.9, 152.1, 147.3, 141.4, 138.8, 135.9, 131.4, 129.8, 129.3, 128.9, 128.8, 128.2, 127.5, 126.4, 123.8, 62.0, 52.2, 42.2, 40.7, 39.8, 31.1, 25.8, 16.1; IR (neat) 1835, 1738, 1709 cm^{-1}; MS *m/z* (%) 495 (20), 451 (13), 335 (5), 334 (11), 149 (17), 117 (80), 91 (100), 65 (67); EI-HRMS calcd. for $C_{29}H_{25}N_3O_5$ $[M]^+$ *m/z* 495.1794, found 495.1764.

23d : Prepared by following general procedure C, using **22c** (12 mg, 37 μmol), diethyl fumarate (0.12 mL). The toluene was removed under vacuum and the crude residue purified by flash chromatography to afford **23d** (7.5 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.38 (m, 5H), 6.38 (q, *J* = 14.8, 7.4 Hz, 1H), 5.75 (m, 1H), 4.59 (d, *J* = 15.1 Hz, 1H), 4.66 (d, *J* = 15.1 Hz, 1H), 3.96-4.29 (m, 5H), 3.29 (m, 1H), 2.77 (m, 1H), 2.63 (m, 1H), 2.48 (m, 1H), 2.16 (d, *J* = 7.4 Hz, 3H), 1.7 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 171.2, 161.2, 151.5, 147.7, 140.7, 138.9, 132.2, 131.9, 128.6, 127.9, 127.2, 125.5, 61.9, 61.8, 61.5, 51.8, 42.2, 42.0, 40.1, 32.4, 24.8, 15.8, 14.4, 14.2; IR (neat) 1839, 1732 cm^{-1}; MS *m/z* (%) 495 (33), 494 (97), 424 (20), 291 (36), 189 (43), 91 (100); EI-HRMS calcd. for $C_{27}H_{30}N_2O_7$ $[M]^+$ *m/z* 494.2053, found 494.2056.

23e : Prepared by following general procedure C, using **22c** (0.136 g, 0.421 mmol), *p*-benzoquinone (0.091 g, 0.84 mmol). The toluene was removed under vacuum and the crude residue purified by flash chromatography to afford **23e** (0.041 g, 23%).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.34 (m, 5H), 6.32-6.40 (m, 2H), 6.21(d, *J* = 10.2 Hz, 1H), 5.63 (q, *J* = 3.3 Hz, 1H), 4.64 (d, *J* = 12.9Hz, 1H), 4.44 (d, *J* = 12.9 Hz, 1H), 4.05 (t, *J* = 4.3 Hz, 1H), 3.12 (m, 1H), 2.78 (m, 1H), 2.46 (m, 1H), 2.25 (m, 1H), 2.20 (d, *J* = 7.3 Hz, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 198.1, 161.2, 152.3, 147.5, 141.6, 139.7, 138.3, 137.7, 132.9, 132.4, 128.9, 128.7, 127.5, 124.2, 61.4, 52.4, 47.7, 47.3, 44.6, 32.7, 27.3, 15.9; IR (neat) 1838, 1728, 1682 cm^{-1}; MS *m/z* (%) 430 (30), 371 (20), 269 (100), 91 (92); EI-HRMS calcd for $C_{25}H_{22}N_2O_5$ $[M]^+$ *m/z* 430.1529, found 430.1526.

23f : Prepared by following general procedure C, using **22c** (0.033 g, 0.102 mmol), dimethylacetylene dicarboxylate (0.15 mL). The toluene was removed under vacuum and the crude residue purified by flash chromatography to afford **23f** (0.011 g, 24%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.34 (m, 5H), 6.48 (q, *J* = 7.5 Hz 1H), 5.81 (bs, 1H), 4.62 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 3.88 (m, 1H), 3.78 (s, 3H), 3.48 (s, 3H), 3.23 (m, 1H), 2.92 (m, 1H), 2.26 (d, *J* = 7.4 Hz, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 166.1, 161.9, 149.8, 147.4, 144.0, 138.6, 138.4, 132.9, 132.5, 128.5, 128.2, 128.1, 126.6, 123.1, 64.7, 52.6, 52.1, 51.9, 45.9, 33.5, 30.1, 16.1; IR (neat) 1834, 1737 cm^{-1}; MS *m/z* (%) 464 (73), 433 (30), 420 (35), 260 (37), 201 (32), 173 (76), 89 (100); EI-HRMS calcd for $C_{25}H_{24}N_2O_7$ $[M]^+$ *m/z* 464.1584, found 464.1595.

24 : A solution of diene (**23c**) (0.020 g, 0.040 mmol) and diethyl fumarate (0.5 ml) in toluene (1 mL) and CH_2Cl_2 (0.6 mL) was heated to 90 ºC until the starting material was completely consumed as evidenced by TLC analysis. The volatiles were removed in vacuo and the crude residue was purified by flash chromatography (hexanes-EtOAc, 4 : 1 to 0 : 1, v/v) to afford **24** (0.019 g, 70%) as an 8 : 1 mixture of diastereomers. (**24** - major diastereomer) : ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12-7.49 (m, 10H), 4.74 (d, *J* = 14.3 Hz, 1H), 4.62 (d, *J* = 14.3 Hz, 2H), 4.14-4.28 (m, 4H), 3.60 (m, 1H), 3.33-3.40 (m, 1H), 3.20 (dd, *J* = 11.1, 6.3 Hz, 1H), 3.02 (m, 1H), 2.81 (t, *J* = 11.1 Hz, 1H), 2.15-2.25 (m, 2H), 1.98 (m, 1H), 1.65 (bs, 1H), 1.24-1.32 (m, 9H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 176.2, 172.3, 171.9, 158.1, 152.2, 146.8, 145.8, 138.5, 133.5, 131.2, 129.5, 129.2, 128.8, 128.3, 127.6, 126.1, 61.6, 61.4, 59.3, 52.4, 48.1, 43.3, 42.0, 39.9, 39.5, 37.9, 32.2, 29.9, 25.3, 18.2, 14.4, 14.3; IR (neat) 1828, 1732, 1712 cm^{-1}; MS *m/z* (%) 667 (20), 652 (6), 506 (25), 433 (26), 359 (14), 317 (6), 212 (11), 143 (15), 117 (22), 91 (100); EI-HRMS calcd for $C_{37}H_{37}N_3O_9$ $[M]^+$ *m/z* 667.2530, found 667.2487.

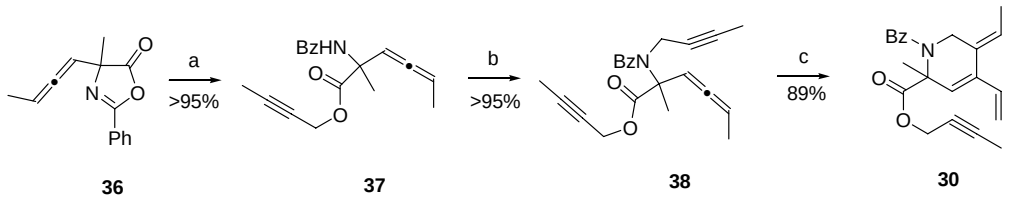
25a : To a solution of **23a** (10 mg, 18 μmol) in 1,2-dichloroethane (100 μL), were added ethyl vinyl ether (50 μL) and $Eu(fod)_3$ (2 mg, 2 μmol). The reaction vessel was then sealed and placed in a sonicator (Branson 2510), and sonication was continued at rt for 6h. The reaction mixture was purified by flash chromatography (hexanes-EtOAc, 1 : 1, v/v) to afford **25a** (11 mg, >95%). ^{1}H NMR (300 MHz, $CDCl_3$):

δ 7.39-7.28 (m, 6H), 7.14-7.07 (m, 4H), 5.72-5.65 (m, 1H), 5.30 (t, *J* = 2.6 Hz, 1H), 4.35 (d, *J* = 18.1 Hz, 1H), 4.20 (d, *J* = 18.1 Hz, 1H), 4.21 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.87-3.76 (m, 1H), 3.79 (s, 3H), 3.58 (dq, *J* = 9.9, 7.1 Hz, 1H), 3.45-3.43 (m, 1H), 3.42 (d, *J* = 13.4 Hz, 1H), 3.09 (d, *J* = 13.4 Hz, 1H),3.07 (bs, 1H), 2.99 (dd, *J* = 15.2, 7.7 Hz, 1H), 2.81 (dt, *J* = 10.3, 6.9 Hz, 1H), 2.41-2.31 (m, 1H), 2.28 (ddd, *J* = 13.9, 6.7, 2.5 Hz, 1H), 1.86-1.77 (m, 1H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, toluene-d^8) δ 177.7, 176.1, 170.1, 156.0, 146.4, 137.9, 134.5, 132.9, 132.7, 130.7, 128.7, 128.1, 126.8, 116.0, 99.6, 97.4, 66.1, 64.5, 51.4, 40.0, 45.0, 44.7, 42.1, 41.8, 37.0, 26.0, 21.4, 21.2, 20.4, 19.7, 14.7; IR (neat) 2594, 1822, 1735, 1712 cm^{-1}; MS *m/z* (%) 649 (50), 648 (100), 576 (15); HRMS calcd. for $C_{35}H_{35}N_3O_8Na$ $[M+23]^+$ *m/z* 648.2322, found 648.2310.

26a : A solution of **25a** (11 mg, 18 μmol) in $CDCl_3$ was allowed to stand at rt for 24 h (slow hydrolysis to **26a** was catalyzed by traces of acid in $CDCl_3$). The solvent was removed under vacuum to afford **26a** (11mg, >95%). Alternatively, addition of 1M HCl (50 μL), accelerates the hydrolysis to 3 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.48-7.31 (m, 6H), 7.18-7.16 (m, 2H), 7.08-7.06 (m, 2H), 4.36 (d, *J* = 18.0 Hz, 1H), 4.37-4.34 (m, 1H), 4.21 (d, *J* = 18.1 Hz, 1H), 3.79 (s, 3H), 3.44-3.31 (m, 7H), 2.87 (dd, *J* = 19.1, 6.2 Hz, 1H), 2.72 (dd, *J* = 19.2, 5.7 Hz, 1H), 2.60-2.46 (m, 1H), 2.28-2.13 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 176.8, 175.8, 170.1, 158.3, 153.6, 147.7, 146.0, 134.2, 132.0, 131.1, 130.0, 128.9, 128.5, 128.4, 125.8, 64.5, 52.2, 49.0, 48.9, 47.4, 41.2, 40.6, 39.8, 27.0, 26.6, 20.2, 18.5; IR (thin film) ν 2954, 2256, 1838, 1743, 1710 cm^{-1}.

26c : The procedure for formation of **25a** was followed using **23c** (9 mg, 18 μmol), ethyl vinyl ether (0.8 mL), and $Eu(fod)_3$ (1.5 mg, 1.5 μmol) to obtain **25c** (9 mg, 93%) which hydrolyzed to **26c** in wet $CDCl_3$. ^{1}H NMR (300MHz, $CDCl_3$): δ 9.55 (s, 1H), 7.16–7.45 (m, 10H), 4.76 (d, *J* = 14.6 Hz, 1H), 4.65 (d, *J* = 14.6 Hz, 1H), 3.96 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.25 (m, 2H), 3.04-3.15 (m, 3H), 2.86 (dd, *J* = 19.1, 6.5 Hz, 1H), 2.67 (m, 1H), 2.51 (m, 1H), 2.12 (m, 1H), 1.78(s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 200.9, 176.9, 175.8, 158.6, 151.9, 147.1, 147.0, 138.7, 134.5, 131.4, 129.3, 128.9, 128.8, 128.3, 127.6, 125.9, 60.4, 52.3, 49.3, 42.0, 40.9, 40.1, 29.9, 27.4, 26.9, 20.2, 18.6; IR (neat) 2251, 1831, 1739, 1709 cm^{-1}; MS *m/z* (%) 539 (83), 521 (60), 511 (45), 495 (50), 469 (33), 379 (35), 350 (65), 91 (100); EI-HRMS calcd. for $C_{31}H_{29}N_3O_6$ $[M]^+$ *m/z* 539.2056, found 539.2068.

30 : Synthesized according to the following scheme:



a) 2-butyne-1-ol (2 equiv.), Et_3N (cat.); b) NaH (2 equiv.), 1-bromo-2-butyne (2 equiv.), DMF; c) 5 mol% $[Rh(CO)_2Cl]_2$, toluene, rt.

37: 2-Butyn-1-ol (0.170 mL, 2.23 mmol) was added to neat **36**[33] (0.253 g, 1.11 mmol) followed by

addition of Et_3N (10 μL) and the reaction was stirred for 30 min. All volatiles were removed under vacuum, and the remaining yellow residue was purified by flash chromatography (hexanes/EtOAc, 4 : 1, v/v) to afford **37** (0.320 mg, 96% as a mixture of inseparable diastereomers in 1.5 : 1 ratio). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.75 (m, 2H), 7.50-7.38 (m, 3H), 6.93 (bs, 0.4H), 6.90 (bs, 0.6H), 5.56-5.38 (m, 2H), 4.80-4.64 (m, 2H), 1.83-1.81 (m, 3H), 1.79 (s, 1.2H), 1.77 (s, 1.8H), 1.73-1.69 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 202.9, 171.9, 171.8, 166.3, 166.3, 134.3, 131.4, 128.4, 128.2, 126.9, 94.0, 91.6, 83.3, 83.2, 72.8, 72.8, 58.4, 54.0, 54.0, 23.0, 22.9, 13.9, 13.9, 3.5; IR (thin film) ν 3308, 2322, 2923, 2243, 2117, 1968, 1744, 1640 cm^{-1}; MS *m/z* (%) 297 (38), 282 (21), 244 (73), 200 (55), 105 (100); EI-HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365; found 297.1364.

38 : A solution of **37** (0.320 g, 1.08 mmol) in dimethylformamide (8 mL) was cooled to 0 °C, and NaH (95% wt) (0.056 g, 2.23 mmol) was added in one portion. After 2 min, 1-bromo-2-butyne (0.195 mL, 2.230 mmol) was added and the reaction mixture was stirred for 30 min at rt. The reaction mixture was then carefully poured over cold water (100 mL), and the aqueous layer was extracted with EtOAc (2 x 50 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, and concentrated under vacuum to afford **38** (0.415 g, >95% as a mixture of inseparable diastereomers in 1.5 : 1 ratio). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.59 (m, 2H), 7.42-7.38 (m, 3H), 5.73-5.66 (m, 1H), 5.42-5.34 (m, 1H), 4.77-4.65 (m, 2H), 4.05-4.01 (m, 2H), 1.85-1.83 (m, 6H), 1.76-1.71 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 205.2, 171.8, 171.7, 171.3, 136.0, 129.9, 128.3, 128.2, 127.1, 127.0, 92.5, 92.4, 90.2, 90.1, 82.8, 82.7, 80.3, 76.0, 73.4, 64.2, 64.0, 53.6, 53.6, 37.5, 37.4, 20.6, 20.6, 13.8, 13.7, 3.6, 3.5; IR (thin film) ν 2921, 2242, 1967, 1746, 1643 cm^{-1}; MS *m/z* (%) 349 (21), 296 (50), 268 (48), 252 (35), 105 (100); EI-HRMS calcd for $C_{22}H_{23}NO_3$ *m/z* $[M]^+$ 349.1678; found 349.1685.

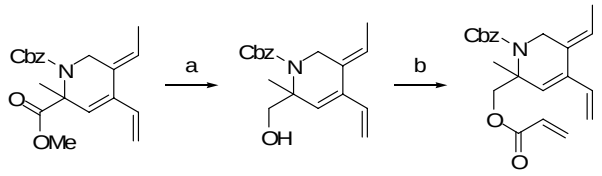
30 : To a solution of **38** (0.173 g, 0.495 mmol) in toluene (5 mL) was added $[Rh(CO)_2Cl]_2$ (7 mg, 17 μmol) under N_2 atmosphere. The light yellow solution was stirred at rt for 1 h when it was directly applied to a silica gel column and eluted (gradient elution, hexanes-EtOAc, 1 : 0 to 4 : 1, v/v) to afford **30** (0.154 g, 89%) after removal of the solvents. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.39 (m, 5H), 6.36 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.78 (q, *J* = 7.1 Hz, 1H), 5.61 (s, 1H), 5.46 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.22 (dd, *J* = 10.7, 1.7 Hz, 1H), 4.75 (dq, *J* = 15.2, 2.3 Hz, 1H), 4.61 (dq, *J* = 15.2, 2.3 Hz, 1H), 4.45 (d, *J* = 14.6 Hz, 1H), 3.70 (d, *J* = 14.6 Hz, 1H), 1.81 (t, *J* = 2.3 Hz, 3H), 1.78 (s, 3H), 1.62 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 137.5, 136.0, 134.3, 130.2, 130.0, 128.5, 127.5, 124.7, 122.8, 117.8, 82.8, 73.4, 62.8, 53.8, 43.5, 20.7, 13.3, 3.6; IR (thin film) ν 2921, 2242, 1743, 1642, 1412, 1106 cm^{-1}; MS *m/z* (%) 349 (17), 284 (5), 252 (40), 105 (100). EI-HRMS calcd for $C_{22}H_{23}NO_3$ *m/z* $[M]^+$ 349.1678; found 349.1674.

31 : To a solution of **30** (15 mg, 43 μmol) in 1,2-dichloroethane (0.5 mL), was added $[Rh(dppe)Cl]_2$[32] (4 mg, 4 μmol), and $AgSbF_6$ (172 μL of a 0.05 M solution in 1,2-dichloroethane, 8 μmol). The reaction

was heated to 95 °C for 12 h. After cooling to room temperature the reaction mixture was directly applied to a silica gel column and eluted (hexanes-EtOAc, 1 : 1, v/v), to afford **31** (10 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.74 (m, 2H), 7.52-7.40 (m, 3H), 7.14 (q, *J* = 1.6 Hz, 1H), 6.39 (bs, 1H), 5.90 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.84 (q, *J* = 6.9 Hz, 1H), 5.38 (d, *J* = 17.3 Hz, 1H), 5.26 (d, *J* = 10.7 Hz, 1H), 4.20 (dd, *J* = 14.5, 5.8 Hz, 1H), 4.11 (dd, J = 14.5, 5.8 Hz, 1H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.85 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 166.8, 149.6, 135.4, 134.2, 131.4, 130.3, 129.0, 128.6, 128.3, 126.8, 116.9, 90.5, 35.9, 13.9, 10.7; IR (thin film) ν 3344, 2924, 1758, 1639 cm^{-1}; MS *m/z* (%) 297 (81), 252 (38), 192 (49), 174 (84), 105 (100). EI-HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365; found 297.1379.

32 : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.71 (bs, 1H), 7.55-7.39 (m, 5H), 6.33 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.78 (q, *J* = 7.1 Hz, 1H), 5.62 (s, 1H), 5.47 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.21 (dd, *J* = 10.7, 1.3 Hz, 1H), 4.41 (d, *J* = 14.5 Hz, 1H), 3.71(d, *J* = 14.5 Hz, 1H), 1.75 (s, 3H), 1.60 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 171.6, 137.4, 135.5, 134.0, 130.4, 129.6, 128.5, 127.5, 124.6, 123.1, 118.0, 62.8, 43.7, 20.6, 13.3; IR (thin film) ν 2983, 2025, 1742, 1593 cm^{-1}; MS *m/z* (%) 297 (7), 253 (67), 252 (80), 105 (100). EI-HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365; found 297.1372.

33 : Synthesized according to the following scheme:



14 **39** **33**

a) diisobutylaluminum hydride (3 equiv.), CH_2Cl_2, -78 °C-rt; b) acryloyl chloride (1.2 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2.

39: A solution of **14** (0.050 g, 0.15 mmol), in toluene (1 mL), was cooled to -50 °C and diisobutylaluminum hydride (0.440 mL of a 1.0M solution in hexanes, 0.440 mmol), was added dropwise. The reaction was allowed to warm up to room temperature over a period of 1 h, when it was quenched by addition of MeOH (0.1 mL) and NH_4Cl aq (0.5 mL). The precipitate was filtered and washed with CH_2Cl_2. After removal of the solvents under vacuum, the crude residue was purified by flash chromatography (hexanes-EtOAc, 4 : 1, v/v) to afford **39** (0.030 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.33 (m, 5H), 6.34 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.69 (q, *J* = 7.0 Hz, 1H), 5.46-5.40 (m, 2H), 5.22-5.13 (m, 2H), 4.71 (d, *J* = 14.3 Hz, 1H), 3.97-3.90 (m, 1H), 3.78 (d, *J* = 14.3 Hz, 1H), 3.66 (d, *J* = 9.0 Hz, 1H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 136.7, 136.4, 134.5, 130.2, 129.4, 128.5, 128.0, 127.7, 122.1, 116.8, 69.0, 67.3, 61.5, 41.3, 20.2, 13.4; IR (thin film) ν 3427, 2927, 1685, 1406 cm^{-1}; MS *m/z* (%) 313 (32), 282 (45), 238 (29), 192 (30), 91 (100); EI-HRMS calcd for $C_{18}H_{20}NO_2$ *m/z* $[M-31]^+$ 282.1494; found 282.1485.

33 : To a solution of alcohol **39** (0.030 g, 0.096 mmol), in CH_2Cl_2 (0.5 mL) was added Et_3N (0.016 mL,

0.11 mmol), followed by acryloyl chloride (0.010 mL, 0.11 mmol) at rt. After 10 min at rt, the reaction was diluted with benzene (0.5 mL) and purified by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) to afford ester (**33**) (0.018 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.34 (m, 5H), 6.37-6.28 (m, 1H), 6.31 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.04 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.77 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.66 (q, *J* = 7.1 Hz, 1H), 5.44 (s, 1H), 5.39 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.14 (dd, *J* = 10.7, 1.8 Hz, 1H), 4.79 (d, *J* = 10.9 Hz, 1H), 4.40-4.34 (m, 2H), 4.18 (d, *J* = 14.3 Hz, 1H), 1.78 (d, J = 6.9 Hz, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 155.2, 136.6, 136.3, 134.5, 130.7, 130.1, 128.6, 128.5, 128.2, 127.9, 127.7, 121.9, 116.8, 67.5, 67.0, 58.6, 42.0, 22.8, 13.4; IR (thin film) ν 2924, 1727, 1699, 1403 cm^{-1}; MS *m/z* (%) 367 (40), 282 (66), 238 (45), 91 (100); EI-HRMS calcd for $C_{22}H_{25}NO_4$ *m/z* $[M]^+$ 367.1784; found 367.1775.

34 : A solution of tetraene (**33**) (0.120 g, 0.327 mmol) in dimethylsulfoxide (60 mL), was heated at 80 °C for 8 h. The solution was then allowed to cool to room temperature and diluted with 120 mL of water. The cloudy mixture was extracted with Et_2O (3 x 70 mL), the extracts were combined and washed with water (100 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (hexanes-EtOAc, 1 : 1, v/v) afforded **34** (0.052 g, 43%). ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.41-7.32 (m, 5H), 6.34 (bs, 1H), 5.93 (q, *J* = 7.1 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 5.00 (d, *J* = 14.9 Hz, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 3.96 (d, *J* = 10.8 Hz, 1H), 3.56 (d, *J* = 14.9 Hz, 1H), 3.10 (dt, *J* = 6.6, 3.8 Hz, 1H), 3.00-2.97 (m, 1H), 2.49 (dq, *J* = 12.9, 3.4 Hz, 1H), 2.14-2.11 (m, 2H), 1.72 (s, 3H), 1.71 (d, *J* = 7.1 Hz, 3H), 1.55 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 172.0, 154.6, 136.2, 131.8, 128.6, 128.2, 128.0, 121.8, 116.9, 70.5, 67.4, 55.5, 42.0, 40.1, 37.0, 24.4, 21.0, 19.6, 13.4; IR (thin film) ν 2920, 1732, 1693, 1403, 1354, 1221, 1167, 1053 cm^{-1}; MS *m/z* (%) 367 (10), 316 (15), 276 (23), 129 (62), 91 (100); EI-HRMS calculated for $C_{22}H_{25}NO_4$ *m/z* $[M]^+$ 367.1784; found 367.1785.

Preparation of cycloadduct (35a) (General procedure D). To a solution of diene (**34**) (10 mg, 27 μmol) in toluene (0.5 mL) was added 4-phenyl-1,2,4-triazoline-3,5-dione (5 mg, 27 μmol) and the reaction was stirred at rt for 10 min. The reaction mixture was directly purified by flash chromatography (hexanes/EtOAc, 4 : 1 to 1 : 1, v/v) to afford **35a** (15 mg, >95%).

35a : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.28 (m, 10H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 4.62-4.57 (m, 1H), 4.51-4.41 (m, 2H), 4.20-4.14 (m, 1H), 3.64 (d, *J* = 15.4, 1H), 3.26-3.17 (m, 1H), 3.00-2.96 (m, 1H), 2.86-2.81 (m, 1H), 2.07-1.95 (m, 1H), 1.75 (s, 3H), 1.71-1.59 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 154.7, 154.6, 150.5, 135.8, 131.0, 130.8, 129.1, 128.8, 128.5, 128.4, 128.3, 128.3, 125.6, 72.8, 67.9, 56.1, 54.1, 51.1, 42.8, 42.3, 33.6, 23.4, 21.7, 19.4, 16.4; IR (thin film) ν 2928, 1772, 1713, 1415 cm^{-1}; MS *m/z* (%) 542 (18), 451 (32), 91 (100); EI-HRMS calcd for $C_{30}H_{30}N_4O_6$ *m/z* $[M]^+$ 542.2165; found 542.2181.

35b : Prepared by following general procedure D, using **34** (10 mg, 27 μmol), *N*-phenylmaleimide (7

mg, 40 μmol). Reaction time (6 h at rt). Isolated yield **35b** (15 mg, >95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.33 (m, 8H), 7.14-7.09 (m, 2H), 5.31 (d, *J* = 11.8 Hz, 1H), 5.13 (s, 2H), 4.44 (d, J = 18.1 Hz, 1H), 4.13 (d, *J* = 11.8 Hz, 1H), 3.67 (dq, *J* = 18.1, 2.2 Hz, 1H), 3.30 (dd, *J* = 8.5, 6.3 Hz, 1H), 3.19 (dd, *J* = 8.5, 5.2 Hz, 1H), 3.13-3.04 (m, 1H), 2.69-2.61 (m, 2H), 2.45 (bs, 1H), 2.30-2.17 (m, 1H), 2.13-1.90 (m, 2H), 1.54 (d, *J* = 7.3 Hz, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 176.2, 173.8, 155.9, 136.2, 132.1, 131.5, 129.1, 128.6, 128.6, 128.1, 127.7, 127.4, 126.1, 71.1, 67.3, 56.1, 46.4, 44.4, 42.1, 41.6, 36.9, 33.0, 23.3, 21.8, 20.7, 12.9, 1.0; IR (thin film) ν 2940, 1747, 1706, 1381 cm^{-1}; MS *m/z* (%) 540 (8), 495 (37), 449 (29), 405 (65), 91 (100); EI-HRMS calcd for $C_{32}H_{32}N_2O_6$ *m/z* $[M]^+$ 540.2260; found 540.2281.

35c : Prepared by following general procedure D, using **34** (18 mg, 49 μmol), maleic anhydride (7 mg, 71 μmol). Reaction time (3 h at rt). Isolated yield **35c** (18 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.13 (s, 2H), 4.37 (d, *J* = 18.0 Hz, 1H), 4.14 (d, *J* = 11.9 Hz, 1H), 3.69 (d, *J* = 16.5 Hz, 1H), 3.40 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.30 (dd, *J* = 9.1, 4.8 Hz, 1H), 3.08 (q, *J* = 8.1 Hz, 1H), 2.64-2.62 (m, 1H), 2.41 (bs, 1H), 2.10-1.89 (m, 2H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 171.2, 171.1, 155.8, 136.9, 132.8, 128.6, 128.1, 128.1, 127.8, 71.5, 67.5, 56.1, 47.2, 45.1, 42.1, 41.7, 36.5, 35.6, 32.3, 22.7, 22.1, 20.4, 12.5; IR (thin film) ν 2947, 1775, 1746, 1705 cm^{-1}; MS *m/z* (%) 465 (10), 437 (28), 330 (38), 91 (100); EI-HRMS calcd for $C_{26}H_{27}NO_7$ *m/z* $[M]^+$ 465.1788; found 465.1782.

35d : Prepared by following general procedure D, using **34** (10 mg, 27 μmol), dimethylacetylenedicarboxylate (10 μL, 81 μmol). Reaction time (10 h at 35 °C). Isolated yield **35d** (13 mg, 94%) as a mixture of diastereomers in 4 : 1 ratio (determined by HPLC). **35d** (data reported for mixture of diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.19-5.08 (m, 2H), 4.76 (d, *J* = 12.8 Hz, 1H), 4.52-4.34 (bs, 1H), 4.26-4.06 (m, 2H), 3.78 (s, 6H), 3.64 (d, *J* = 16.6 Hz, 1H), 3.28 (t, *J* = 6.2 Hz, 1H), 3.04-2.92 (m, 2H), 2.81-2.73 (m, 1H), 2.68 (s, 1H), 2.31-2.14 (m, 1H), 1.75 (s, 3H), 1.46-1.32 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H). IR (thin film) ν 2925, 1725, 1693, 1257 cm^{-1}; MS *m/z* (%) 509 (10), 494 (27), 478 (40), 386 (80), 91 (100); EI-HRMS calcd for $C_{28}H_{31}NO_8$ *m/z* $[M]^+$ 509.2050; found 509.2059.

ACKNOWLEDGEMENTS

We are grateful to the National Institutes of Health (NIGMS) for financial support (P50 GM067982). We thank Dr. Steven Geib for performing X-ray crystallography. Dr. Stefan Werner (University of Pittsburgh-CMLD) is acknowledged for collaboration efforts in the early stages of this work. KMB thanks Johnson & Johnson for a Focused Giving Award and University of Pittsburgh for a Chancellor's Distinguished Research Award. BM thanks the University of Pittsburgh for an Andrew Mellon Predoctoral Fellowship.

REFERENCES (AND NOTES)

1. (a) I. Nakamura and Y. Yamamoto, *Chem. Rev*., 2004, **104**, 2127. (b) C. Aubert, O. Buisine, and M. Malacria, *Chem. Rev*., 2002, **102**, 813. (c) I. Ojima, M. Tzamarioudaki, Z. Li, and R. J. Donovan., *Chem. Rev*., 1996, **96**, 635.
2. (a) T. Kobayashi, Y. Koga, and K. Narasaka, *J. Organomet. Chem*., 2001, **624**, 73. (b) N. Jeong, S. Lee, and B. K. Sung, *Organometallics*, 1998, **17**, 3642.
3. P. A. Wender, L. O. Houstedt, J. Lim, J. A. Love, T. J. Williams, and J. –Y. Yoon, *J. Am. Chem. Soc*., 2006, **128**, 6302.
4. S. –J. Paik, S. U. Son, and Y. K. Chung, *Org. Lett*., 1999, **1**, 2045.
5. P. Cao, B. Wang, and X. Zhang, *J. Am. Chem. Soc*., 2000, **122**, 6490.
6. K. M. Brummond, H. Chen, P. Sill, and L. You, *J. Am. Chem. Soc*., 2002, **124**, 15186.
7. K. M. Brummond and B. Mitasev, *Org. Lett*., 2004, **6**, 2245.
8. K. M. Brummond and L. You, *Tetrahedron*, 2005, **61**, 6180.
9. (a) M. D. Burke and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.,* 2004, **43**, 46. (b) S. L. Schreiber, *Science*, 2000, **287**, 1964. (c) A. B. Beeler, S. E. Schaus, and J. A. Porco Jr, *Curr. Opin. Chem. Biol*., 2005, **9**, 277; (d) D. S. Tan, *Nat. Chem. Biol*., 2005, **1**, 74.
10. (a) K. M. Brummond, D. P. Curran, B. Mitasev, and S. Fischer, *J. Org. Chem.,* 2005, **70**, 1745. (b) S. Werner, P. S. Iyer, M. D. Fodor, C. M. Coleman, L. A. Twining, B. Mitasev, and K. M. Brummond, *J. Comb. Chem*., 2006, **8**, 368.
11. (a) O. Tsuge, E. Wada, and S. Kanemasa, *Chem. Lett.,* 1983, 239. (b) O. Tsuge, E. Wada, and S. Kanemasa, *Chem. Lett.,* 1983, 1525.
12. (a) S. Woo, N. Squires, and A. G. Fallis, *Org. Lett.,* 1999, **1**, 573. (b) S. Woo, S. Legoupy, S. Parra, and A. G. Fallis, *Org. Lett.,* 1999, **1** ,1013.
13. A. D. Payne, A. C. Willis, and M. S. Sherburn, *J. Am. Chem. Soc*., 2005, **127**, 12188.
14. For example, Fallis' methodology was applied by Schreiber and coworkers to the diversity-oriented synthesis of a library of polycyclic small molecules: (a) O. Kwon, S. B. Park, and S. L. Schreiber, *J. Am. Chem. Soc.,* 2002, **124**, 13402. For other applications of heteroatom containing cross-conjugated trienes, see: (b) C. Spino, G. Liu, N. Tu, and S. Girard, *J. Org. Chem*., 1994, **59**, 5596. (c) A. Dion, P. Dubé, and C. Spino, *Org. Lett*., 2005, **7**, 5601.
15. K. M. Brummond, T. O. Painter, D. A. Probst, and B. Mitasev, "Rh(I)-Catalyzed Allenic Carbocyclization Reaction Affording δ- and ε-Lactams" *Submitted for publication.*
16. The structure of **22a** was assigned based on an X-ray of a later intermediate, Diels-Alder product (**23a**).
17. Best yields were obtained when all three reactions were performed without intermediate purification.

See experimental section for details.

18. For the unexpected formation of a similar oxazolidinone, see: T. Granier and A. Vasella, *Helv. Chim. Acta.,* 1998, **81**, 865.
19. Reactions were run until all starting material was consumed. No byproducts were isolated.
20. Reaction was also not observed with the following dienophiles: 2-cyclohexene, 2-cyclopentene, acrolein and methyl-vinyl ketone.
21. (a) G. Tacconi, P. Iadarola, F. Marinone, P. P. Righetti, and G. Desimoni, *Tetrahedron*, 1975, **31**, 1179. (b) A. V. Rudnichenko, V. M. Timoshenko, A. N. Chernega, A. M. Nesterenko, and Y. G. Shermolovich, *J. Fluorine Chem*., 2004, **125**, 1351. (c) M. Burdisso, G. Desimoni, G. Faita, P. Righetti, and G. Tacconi, *J. Chem. Soc., Perkin Trans., 2*, 1989, **7**, 845.
22. For use of $Eu(fod)_3$ to catalyze hetero Diels-Alder reactions, see: (a) M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc*., 1983, **105**, 3716. (b) G. Dujardin, S. Leconte, L. Coutable, and E. Brown, *Tetrahedron Lett*., 2001, **42**, 8849. (c) K. D. Hughes, T. –L. N. Nguyen, D. Dyckman, D. Dulay, W. J. Boyko, and R. M. Giuliano, *Tetrahedron: Asymmetry*, 2005, **16**, 273. (d) G. Dujardin, S. Rossignol, and E. Brown, *Synthesis*, 1998, 763.
23. B. Wang, P. Cao, and X. Zhang, *Tetrahedron Lett*., 2000, **41**, 8041.
24. (a) R. S. Jolly, G. Luedtke, D. Sheehan, and T. Livinghouse, *J. Am. Chem. Soc*., 1990, **112**, 4965. (b) T. Mandai, S. Suzuki, A. Ikawa, T. Murakami, M. Kawada, and J. Tsuji, *Tetrahedron Lett*., 1991, **32**, 7687.
25. For Ag(I)-catalyzed cycization of allenic acids, see: J. A. Marshall, M. A. Wolf, and E. M. Wallace, *J. Org. Chem.,* 1994, **59**, 7169.
26. J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem*., 1977, **42**, 3846.
27. M. Lautens, K. Fagnou, and D. Yang, *J. Am. Chem. Soc*., 2003, **125**, 14884.
28. Recently, a comprehensive study examined the effects contributing to the observed stereochemistry for thermal and Lewis acid catalyzed reactions of relatively unfunctionalized hexadienyl-acrylates. (a) E. L. Pearson, L. C. H. Kwan, C. I. Turner, G. A. Jones, A. C. Willis, M. N. Paddon-Row, and M. S. Sherburn, *J. Org. Chem.,* 2006, **71**, 6099. In general, difficulties associated with Diels-Alder reactions of ester-tethered substrates are attributed to existence of the ester moiety in an unfavorable *transoid* conformation in order to minimize repulsive dipole interactions. For a successful Diels-Alder reaction, the ester needs to rotate into a less favorable *cisoid* conformation that results in increase of the net dipole moment and steric repulsion between the two alkyl groups. (b) P. Deslongchamps, Stereoelectronic Effects in Organic Chemistry; Pergamon: Oxford, 1983; 54-100. Earlier studies have unveiled a dramatic solvent effect on the ester tethered Diels-Alder reaction. (c) M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, 1989, **111**, 5469.

29. (a) A. Alexakis, D. Jachiet, and L. Toupet *Tetrahedron*, 1989, **45**, 6203. (b) C. –Y. Chen and D. J. Hart, *J. Org. Chem.*, 1993, **58**, 3840.
30. Following completion of this work Taguchi has reported two catalytic systems for promoting the Diels-Alder reaction of ester tethered substrates. For $In(OTf)_3$ catalyzed reaction, see: (a) H. Yanai, A. Saito, and T. Taguchi., *Tetrahedron*, 2005, **61**, 7087. And, $TfN[Al(Me)Cl]_2$ catalyzed reaction (b) A. Saito, H. Yanai, and T. Taguchi, *Tetrahedron*, 2004, **60**, 12239.
31. Highest yield (50%) of the tricyclic lactone (**34**) was obtained when the reaction was performed at lower concentrations (0.01M), suggesting that side reactions may be responsible for the low yield (mass spectral analysis of the reaction mixture suggested the presence of dimeric products possibly arising from a Diels-Alder reaction of the more reactive diene in the product with an acrylic ester moiety from a molecule of unreacted starting material). Personal communication from Dr. Stefan Werner.
32. G. E. Ball, W. R. Cullen, M. D. Fryzuk, B. R. James, and S. J. Rettig, *Organometallics*, 1991, **10**, 3767.
33. A. L. Castelhano, S. Horne, G. J. Taylor, R. Billedeau, and A. Krantz *Tetrahedron* 1988, **44**, 5451.