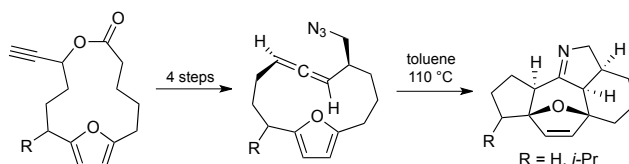


Access to a guanacastepene and cortistatin-related skeleton via ethynyl lactone Ireland–Claisen rearrangement and transannular (4+3)-cycloaddition of an azatrimethylenemethane diyl

Oleksandr Zhurakovskiy,[†] Sam R. Ellis, Amber L. Thompson, and Jeremy Robertson*

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, United Kingdom.

Supporting Information



ABSTRACT: Heating a 2,5-furanocyclic (2-azidoethyl)allene initiates a cascade reaction comprising azide–allene cycloaddition, loss of nitrogen, and azatrimethylenemethane (ATMM) diyl–furan transannular (4+3)-cycloaddition. The major product of this reaction contains the pentacyclic core common to guanacastepenes D and H, and radianspenes J–L; in addition, the central oxa-bridged cycloheptene ring, flanked by two carbocyclic rings, is structurally related to the ABC-ring system found in the cortistatins. This is the first reported synthetic application of a ‘free’ (non-conjugated) ATMM. The cyclization precursors were prepared via the first reported examples of the Ireland–Claisen rearrangement of an ethynyl lactone.

The structural motif of a cycloheptene flanked by two five- or six-membered carbocyclic rings is present in a diverse range of synthetic molecules and natural products, such as cortistatin A, guanacastepene A, and solanoeclepin A (Figure 1). Beyond the intrinsic interest deriving from their often profound biological activity,¹ these molecules continue to provide inspiration to synthetic chemists engaged in the pursuit of powerful new ring-forming reactions.² Herein, we report an approach to this structural class that, for the first time, engages 1,3-diyls³ in transannular cycloaddition reactions.

Our group has shown that rhodium nitrenoids derived from *O*-buta-2,3-dienyl carbamates undergo intramolecular amination, resulting in bicyclic methylene aziridines (MAs). These strained aziridines are converted into 2-amidoallyl cations **2** (Scheme 1) upon acidic treatment that, in turn, may then be intercepted by suitably-disposed dienes, exemplified by the formation of tetracycle **3** from MA **1**.⁴ Building from this work, we explored the possibility that azatrimethylene methane (ATMM) diyls⁵ might behave analogously.⁶ Feldman has shown that the thermal dipolar cycloaddition of azidoethyl allenes leads to loss of dinitrogen and formation of ATMM intermediates that, in the conjugated systems under study, immediately undergo ring-closure, leading to cyclopenta[*b*]pyrrole derivatives (**4**→**5**→**6**, Scheme 2).⁷ We speculated that standalone – that is, non-conjugated – ATMM intermediates would enter into formal cycloaddition reactions with tethered alkenes and dienes resulting in polycyclic products with general application to alkaloid synthesis.⁸ This paper describes preliminary results supporting the viability of this method as a route to structures of the type illustrated in Figure 1.

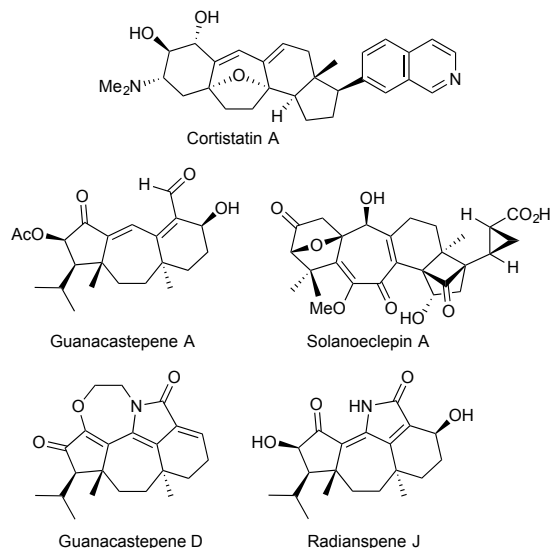
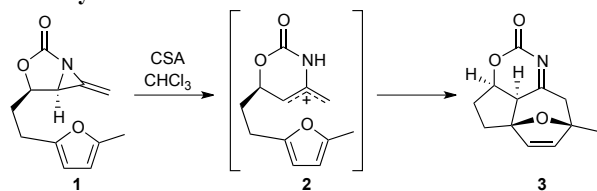


Figure 1. Natural products featuring polycyclic cores with a central 5(6)-7-6 tricyclic system.

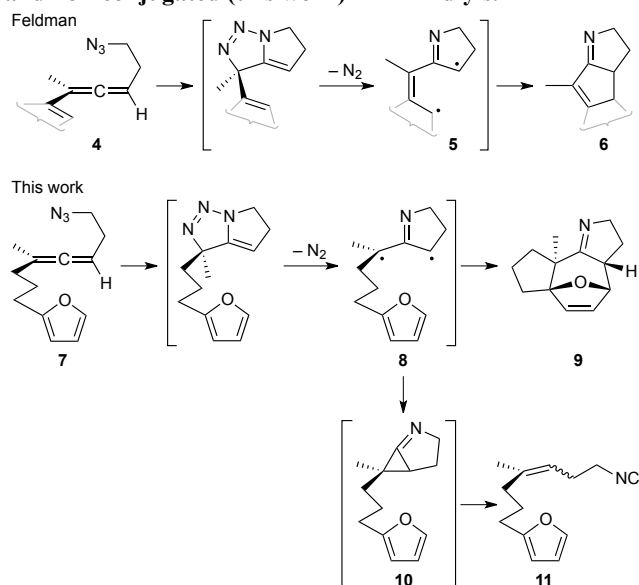
In a first reaction, intended to produce an analogue of intermediate **2**, the isolated azidoethyl allene **7** (X = O) incorporating a furan ring was transformed upon heating into a mixture of two major products, the tetracyclic pyrroline **9** (40%) and isocyanide **11** (9%). We interpret this reaction as proceeding through the mechanism outlined in Scheme 2 with the course of the process partitioning at the ATMM (**8**). Thus, direct trapping by the furan leads to tetracycle **9**, whereas the com-

peting ring closure (\rightarrow **10**) and cheletropic elimination of isocyanide leads to **11**.

Scheme 1. Intramolecular (4+3)-cycloaddition of 2-amidoallyl cations onto tethered furans.



Scheme 2. Divergent behaviors of conjugated (Feldman) and non-conjugated (this work) ATMM diyls.



This preliminary result demonstrated that diyl capture by a tethered furan could compete with isocyanide formation even in a conformationally unbiased substrate. On this basis, we predicted that a transannular variant of the process, in which the reactive diyl and furan functionalities are naturally pre-oriented to combine, would favor cycloaddition over the isocyanide-forming pathway.⁹ Furthermore, such a process would lead in short order to the tricyclic motif central to molecules of the type exemplified in Figure 1 with the added feature of a fused pyrroline. This ring-system is found in five naturally-occurring guanacastepene lactams¹⁰ (exemplified by guanacastepene D and radianspene J in Figure 1) and five advanced

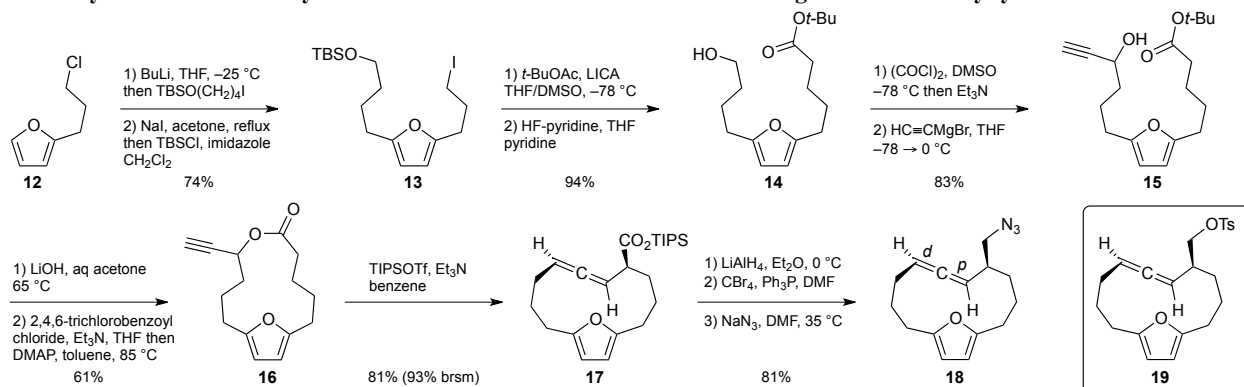
synthetic intermediates described by Carreira.¹¹ We set out to investigate the viability of a transannular ATMM diyl cycloaddition as a strategy for the total synthesis of these lactam diterpenes.

The synthesis of a suitable macrocyclic azidoethyl allene commenced with the preparation of lactone **16** (Scheme 3) from easily accessible furan **12**.¹² Following straightforward alkylation and Finkelstein reactions, extension of the 3-iodopropyl side-chain was conveniently achieved by treating iodide **13** with the enolate of *t*-butyl acetate in THF/DMSO.¹³ In this reaction the enolate is generated in THF with lithium *N*-isopropyl cyclohexylamide (LICA) under conditions that prevent self-condensation of the ester. Dropwise addition of this enolate to a DMSO solution of iodide **13** at rt effected rapid alkylation, and yields in excess of 90% at gram scale were routinely achievable. Ester **14** was converted into lactone **16** in four straightforward steps, terminating with macrolactonisation using Carreira's modification¹⁴ of the Yamaguchi protocol.¹⁵

The intention at this stage was to effect an Ireland–Claisen rearrangement under the soft enolization conditions reported by Brummond for acyclic substrates.¹⁶ Small-scale preliminary experiments failed to produce any allene until it was realized that the reaction concentration was a crucial parameter. The early attempts were run typically at ~0.04 M in substrate, which proved far too dilute for the reactions to progress at a reasonable rate. However, at 0.7 M, the desired rearrangement proceeded smoothly at rt to generate allenic ester **17** in the first example of a macrocyclic alkynyl lactone Ireland–Claisen rearrangement.¹⁷

Silyl ester **17** was obtained initially as a single diastereomer that epimerized slowly upon standing in CDCl₃ (dr = 90:10 after ~12 h). This loss of stereochemical integrity supports a kinetic origin for the stereoselectivity observed in the Ireland–Claisen rearrangement. The stereochemistry, assigned by single crystal X-ray diffraction studies of derivative **19** (Figure 2),¹⁸ is consistent with the pre-transition state models **21** and **21'** (Scheme 4) deriving from the silyl ketene acetals *E*-**20** and *Z*-**20**, respectively, which are expected to be present in equilibrium under the reaction conditions. Hand-held models suggest that the reaction likely proceeds from *E*-**20**. Preliminary computational investigations support this suggestion, with the transition state corresponding to model **21** calculated to be significantly (>30 kJ mol⁻¹) more accessible than all other possibilities (see the Supporting Information for further details).

Scheme 3. Synthesis of azidoethyl allene **18 based on Ireland–Claisen rearrangement of an alkynyl lactone.**



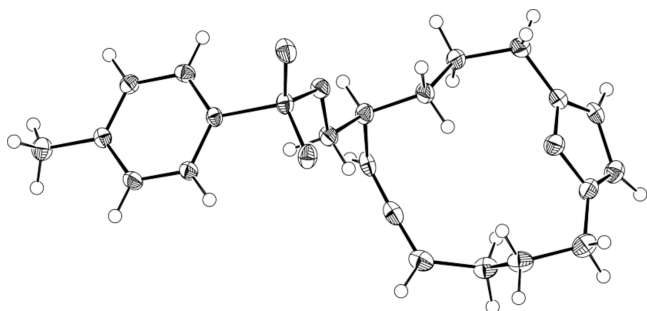
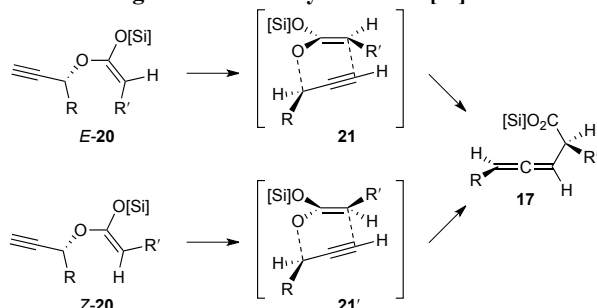


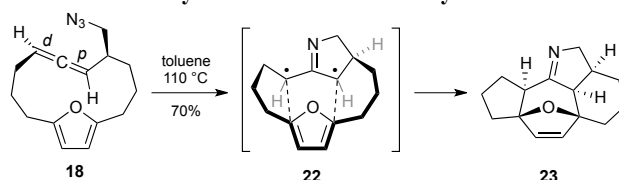
Figure 2. Structure of sulfonate **19** from single crystal diffraction studies. Thermal ellipsoids drawn at 50% probability.¹⁸

Scheme 4. Pre-transition state models connecting both silyl ketene acetal geometries to silyl ester **17**. [Si] = TIPS



Routine functional group manipulations from ester **17** then afforded the target azide **18**. Heating this compound in toluene at 110 °C initiated the cycloaddition-elimination-cycloaddition cascade to afford the desired pentacyclic imine **23** (Scheme 5). The product was formed as a single diastereomer, established to be that shown by NOE experiments. No aromatized triazole was observed despite the distal alkene [(C=C)_d] in **18**] being merely monosubstituted.¹⁹ The imine **23** is prone to decomposition; however, acceptable isolated yields were obtained when the reaction was run at high dilution with rapid chromatographic purification performed directly on the toluene solution of the crude product.

Scheme 5. Cascade azide-allene cycloaddition, ATMM formation and diyl-furan transannular cycloaddition.

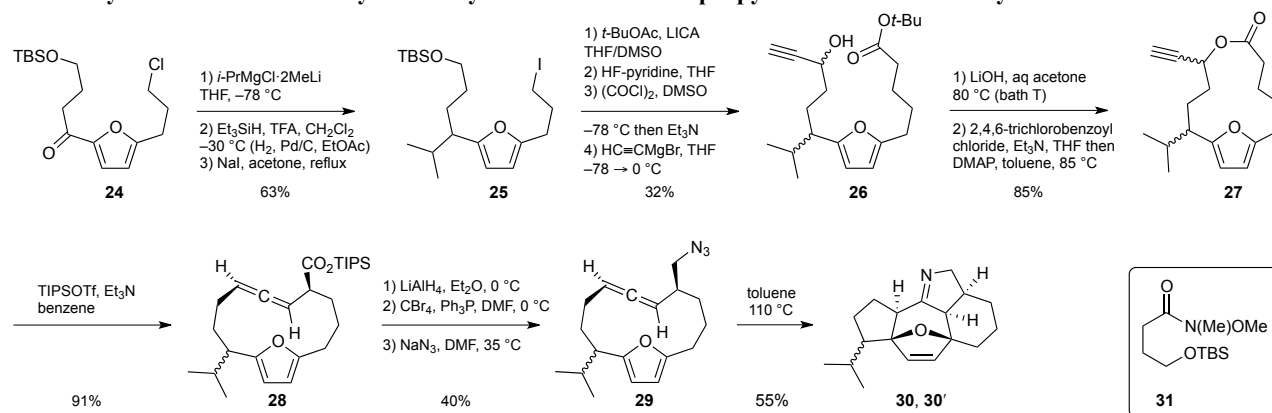


Having achieved a proof-of-principle synthesis of pentacycle **23**, the isopropyl-substituted analog **30** (Scheme 6) was targeted to more closely match the guanacastepene and radianspene cores, and establish if the isopropyl substituent would interfere with the transannular cycloaddition. Ketone **24** was prepared by acylation of furan derivative **12** with Weinreb amide **31**.²⁰ Elaboration of this ketone by a seven-step sequence generated isopropyl-substituted hydroxyester **26** as a 50:50 ratio of diastereomers arising from non-stereoselective alkynylation. Ester hydrolysis, and macrolactonisation as before, delivered lactone **27** efficiently. The Ireland–Claisen rearrangement again proved effective, and just two diastereomers of allene **28** were observed.²¹ Azide **29** was subsequently prepared in a moderate unoptimized yield on small scale. Finally, heating this azide resulted in successful formation of pentacyclic imine **30/30'** with the reduced yield in this case reflecting the greater instability of this imine towards purification by chromatography on silica gel. NOE experiments conducted on the separated diastereomer **30** confirmed that the sense of stereocontrol during the cycloaddition step paralleled that obtained in the nor-isopropyl series and that the two differed merely at the isopropyl centre.

These final compounds (**30**, **30'**) constitute almost complete carbon frameworks of guanacastepene D and radianspene J, lacking only the two cycloheptene methyl substituents. Conceptually, completion of the synthesis of these and related natural products may be achieved by late-stage introduction of the oxy- functionality and unsaturation, and substitution of the oxa- bridge by the methyl groups. These aspects are currently under active investigation in our group, and results from this study will be reported in due course.

In conclusion, this work demonstrates that standalone ATMMs can be generated conveniently from azidoethyl allenes and then employed in rapid secondary processes leading to complex polycyclic structures.

Scheme 6. Synthesis and ATMM diyl-furan cycloaddition of an isopropyl-substituted azidoethyl allene **29**.



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxx. Experimental details and procedures, compound characterization data, copies of ^1H and ^{13}C NMR spectra for all new compounds, crystallographic data, and supporting computation (PDF).

AUTHOR INFORMATION

Corresponding Author

* Email: jeremy.robertson@chem.ox.ac.uk.

Present Addresses

†Current address: School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, United Kingdom.

Author Contributions

JR conceived and supervised the project, OZ and SRE conducted the synthetic chemistry, and ALT produced the crystallographic data. All authors contributed to the production of the manuscript.

ACKNOWLEDGMENT

We thank George Feast and Christopher Brown, University of Oxford, for preliminary experiments, and the Clarendon Fund for partial support of a doctoral studentship (to OZ). We also thank Diamond Light Source for an award of beamtime on I19 (MT7768), and the instrument scientists for support.

REFERENCES

- (1) Isolation and biological activity: Cortistatins: (a) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148; (b) Aoki, S.; Watanabe, Y.; Tanabe, D.; Arai, M.; Suna, H.; Miyamoto, K.; Tsujibo, H.; Tsujikawa, K.; Yamamoto, H.; Kobayashi, M. *Bioorg. Med. Chem.* **2007**, *15*, 6758; (c) Sato, Y.; Kamiyama, H.; Usui, T.; Saito, T.; Osada, H.; Kuwahara, S.; Kiyota, H. *Biosci. Biotech. Biochem.* **2008**, *72*, 2992; Guancastepene A: (d) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, S. *J. Am. Chem. Soc.* **2000**, *122*, 2116; (e) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256; Solanoeclepin A: (f) Schenk, H.; Driessen, R. A. J.; de Gelder, R.; Goubitz, K.; Nieboer, H.; Bruggemann-Rotgans, I. E. M.; Diepenhorst, P. *Croat. Chem. Acta* **1999**, *72*, 593.
- (2) Selected total syntheses: Cortistatins: (a) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864; (b) Nicolaou, K. C.; Sun, Y. P.; Peng, X. S.; Polet, D.; Chen, D. Y. K. *Angew. Chem. Intl. Ed.* **2008**, *47*, 7310; (c) Shen, R. A.; Guerrero, C. A.; Shi, J.; Li, C. C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241; (d) Nicolaou, K. C.; Peng, X. S.; Sun, Y. P.; Polet, D.; Zou, B.; Lim, C. S.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2009**, *131*, 10587; (e) Flyer, A. N.; Si, C.; Myers, A. G. *Nature Chem.* **2010**, *2*, 886; (f) Chen, D. Y. K.; Tseng, C. C. *Org. Biomol. Chem.* **2010**, *8*, 2900 (review); (g) Narayan, A. R. H.; Simmons, E. M.; Sarpong, R. *Eur. J. Org. Chem.* **2010**, 3553 (review); (h) Nilson, M. G.; Funk, R. L. *J. Am. Chem. Soc.* **2011**, *133*, 12451; (i) Shi, J.; Manolikakes, G.; Yeh, C. H.; Guerrero, C. A.; Shen, R. A.; Shigehisa, H.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 8014; (j) Yamashita, S.; Iso, K.; Kitajima, K.; Himuro, M.; Hirama, M. *J. Org. Chem.* **2011**, *76*, 2408; Guancastepene A: (k) Lin, S. N.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem. Intl. Ed.* **2002**, *41*, 2188; (l) Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10619; (m) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025; Solanoeclepin A: (n) Tanino, K.; Takahashi, M.; Tomata, Y.; Tokura, H.; Uehara, T.; Narabu, T.; Miyashita, M. *Nature Chem.* **2011**, *3*, 484.
- (3) For extensive discussion of 1,3-diyl and other diradical species see: (a) Manabu, A. *Chem. Rev.* **2013**, *113*, 7011; for a recent theoretical treatment of trimethylenemethane and its oxa- and aza- variants see: (b) de Wergifosse, M.; Champagne, B.; Ito, S.; Fukuda, K.; Nakano, M. *Phys. Chem. Chem. Phys.* **2016**, *18*, 6420.
- (4) (a) Robertson, J.; Feast, G. C.; White, L. V.; Steadman, V. A.; Claridge, T. D. W. *Org. Biomol. Chem.* **2010**, *8*, 3060; see also (b) Prié, G.; Prévost, N.; Twin, H.; Fernandes, S. A.; Hayes, J. F.; Shipman, M. *Angew. Chem. Intl. Ed.* **2004**, *43*, 6517.
- (5) Such species have been implicated as potential intermediates since the description of the photolysis of allenimines: (a) Brinton, R. K.; *J. Phys. Chem.* **1964**, *68*, 2652; simple ATMMs and related species have been generated by elimination of N_2 from pyrazoline imines to define their general chemistry, see especially: (b) Quast, H.; Fuss, A.; Heublein, A. *Angew. Chem. Intl. Ed.* **1980**, *19*, 49; (c) Quast, H.; Meichsner, G. *Chem. Ber.* **1987**, *120*, 1049.
- (6) O. Zhurakovskiy, *D.Phil. Thesis*, University of Oxford, **2013**.
- (7) (a) Feldman, K. S.; Iyer, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 4590; (b) Feldman, K. S.; Iyer, M. R.; Hester II, D. K. *Org. Lett.* **2006**, *8*, 3113; (c) López, C. S.; Faza, O. N.; Feldman, K. S.; Iyer, M. R.; Hester II, D. K. *J. Am. Chem. Soc.* **2007**, *129*, 7638; (d) Feldman, K. S.; Iyer, M. R.; López, C. S.; Faza, O. N. *J. Org. Chem.* **2008**, *73*, 5090; (e) Feldman, K. S.; Hester II, D. K.; López, C. S.; Faza, O. N. *Org. Lett.* **2008**, *10*, 1665; (f) Feldman, K. S.; Hester II, D. K.; Iyer, M. R.; Munson, P. J. López, C. S.; Faza, O. N. *J. Org. Chem.* **2009**, *74*, 4958; (g) Faza, O. N.; Feldman, K. S.; López, C. S. *Curr. Org. Chem.* **2010**, *14*, 1646; (h) Feldman, K. S.; Antoline, J. F. *Org. Lett.* **2012**, *14*, 934; (i) Feldman, K. S.; Antoline, J. F. *Tetrahedron* **2013**, *69*, 1434; (j) Feldman, K. S.; Gonzalez, I. Y.; Glinkerman, C. M. *J. Am. Chem. Soc.* **2014**, *136*, 15138; (k) Feldman, K. S.; Gonzalez, I. Y.; Glinkerman, C. M. *J. Org. Chem.* **2015**, *80*, 11849; (l) Feldman, K. S.; Folda, T. S. *J. Org. Chem.* **2016**, *81*, 4566; see also (m) Huang, X.; Zhu, S.; Shen, R. *Adv. Synth. Catal.* **2009**, *351*, 3118; (n) Gronnier, C.; Boissonat, G.; Gagosz, F. *Org. Lett.* **2013**, *15*, 4234.
- (8) The sequential formation and cycloaddition of the all-carbon parent, trimethylenemethane, and its derivatives is well developed; selected references: (a) Dowd, P.; Sen Gupta, G.; Sachdev, K. *J. Am. Chem. Soc.* **1970**, *92*, 5726; (b) Berson, J. A.; McDaniel, D. M.; Corwin, L. R.; Davis, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 5508; (c) Dolbier, W. R.; Burkholder, C. R. *Tetrahedron* **1985**, *41*, 297; (d) Little, R. D. *Chem. Rev.* **1996**, *96*, 93; (e) Russu, W. A.; Villalon, V. P.; Wang, V. R.; Miranda, J. A.; Little, R. D. *Tetrahedron Lett.* **2002**, *43*, 8459; (f) Lee, H.-Y. *Acc. Chem. Res.* **2015**, *48*, 2308.
- (9) Cf. (a) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931; (b) Gung, B. W.; Craft, D. T. *Tetrahedron Lett.* **2009**, *50*, 2685; (c) Gung, B. W.; Craft, D. T.; Bailey, L. N.; Kirschbaum, K. *Chem. Eur. J.* **2010**, *16*, 639.
- (10) (a) Guancastepenes D and H: Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900; (b) Radianspenes J, K, and L: Ou, Y.-x.; Li, Y.-y.; Qian, X.-m.; Shen, Y.-m. *Phytochem.* **2012**, *78*, 190.
- (11) Gampe, C. M.; Carreira, E. M. *Chem. Eur. J.* **2012**, *18*, 15761.
- (12) Rogers, C.; Keay, B. A. *Can. J. Chem.* **1992**, *70*, 2929.
- (13) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318.
- (14) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274.
- (15) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
- (16) (a) Brummond, K. A.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186; (b) Brummond, K. M.; You, L. *Tetrahedron* **2005**, *61*, 6180; (c) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. Y. *Tetrahedron Lett.* **1981**, *22*, 3455.
- (17) First reports of analogous rearrangements of open chain alkynyl esters: (a) Hudlicky, T.; Kwart, L. D.; Tiedje, M. H.; Ranu, B. C.; Short, R. P.; Frazier, J. O.; Rigby, H. L. *Synthesis* **1986**, 716; (b) Baldwin, J. E.; Bennett, P. A. R.; Forrest, A. K. *J. Chem. Soc., Chem. Commun.* **1987**, 250.
- (18) Single crystal X-ray diffraction data were collected at 100 K with synchrotron radiation using I19 (EH1) at Diamond Light Source ($\lambda = 0.6889 \text{ \AA}$). Nowell, H.; Barnett, S. A.; Christensen, K. E.; Teat, S.

J.; Allan, D. R. *J. Synch. Rad.* **2012**, *19*, 435). Raw data were reduced using CrysAlisPro. The structure was solved with SuperFlip (Palatinus, L.; Chapuis, G. *J. Appl. Cryst.* **2007**, *40*, 786) and refined using CRYSTALS (Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Cryst.* **2003**, *36*, 1487; Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Cryst.* **2010**, *43*, 1100) as per the SI (CIF). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1531930) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(19) The first-formed azide-allene cycloadducts from substrates in which the distal C=C bond of the allene bears at least one hydrogen

usually isomerize to the stable triazoles during the reaction. (a) Feast, G. C. *D.Phil Thesis*, University of Oxford, **2011**; (b) Brown, C. *Chemistry Part II Thesis*, University of Oxford, **2011**.

(20) Kerr, W. J.; Morrison, A. J.; Paterson, L. C. *Tetrahedron* **2015**, *71*, 5356.

(21) The relative configuration in compound **28** onwards is assumed by analogy to that established for the compounds in Scheme 3. The sample of ester **28** taken on in the sequence was slightly enriched in one epimer at the isopropyl centre (following chromatography), with the result that compounds **29** and **30/30'** were obtained with dr ~60:40.
