Natural Product Synthesis

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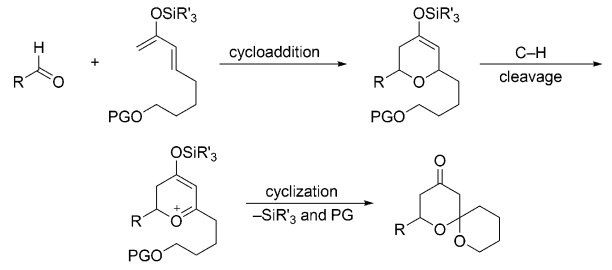
Spiroacetal Formation through Telescoped Cycloaddition and Carbon–Hydrogen Bond Functionalization: Total Synthesis of Bistramide A**

*Xun Han and Paul E. Floreancig**

Abstract: *Spiroacetals can be formed through a one-pot sequence of a hetero-Diels–Alder reaction, an oxidative carbon–hydrogen bond cleavage, and an acid treatment. This convergent approach expedites access to a complex molecular subunit which is present in numerous biologically active structures. The utility of the protocol is demonstrated through its application to a brief synthesis of the actin-binding cytotoxin bistramide A.*

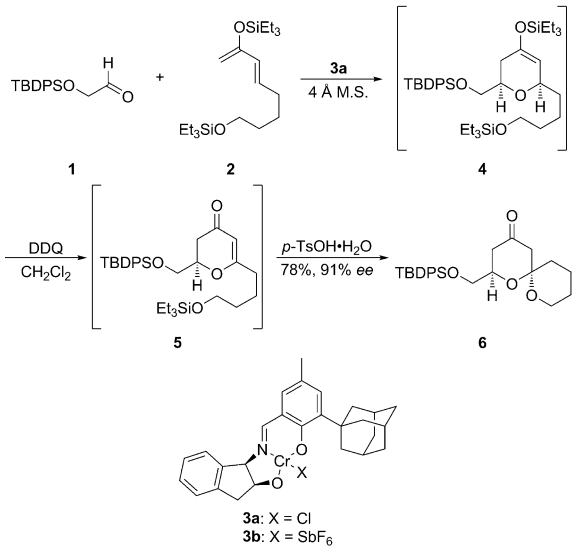
Transformations that generate multiple product-relevant bonds facilitate complex molecule synthesis.[1] Intermolecular cycloaddition reactions such as the hetero-Diels–Alder reaction[2] are ideally suited for this objective. Oxidative carbon–hydrogen bond functionalization[3] also introduces product-relevant bonds from structurally simple precursors. This manuscript describes a telescoped sequence comprising an asymmetric hetero-Diels–Alder reaction and oxidative carbon–hydrogen bond functionalization to access spiroacetals. These units are components of numerous biologically active structures[4] and have inspired multiple synthetic approaches.[5] The mild and convergent protocol described herein provides a step-economical approach to the construction of these structures. The applicability of the sequence to complex molecule synthesis is demonstrated through the total synthesis of the cytotoxin bistramide A.

The strategy is illustrated in Scheme 1. The fragment-coupling phase of this transformation can be achieved through the union of a silyloxy diene with an aldehyde to yield a 4-silyloxy dihydropyran. Related structures have been used as precursors for spiroacetals through multistep sequences.[6,7] However the electron-rich alkene and cation-stabilizing oxygen atom make the dihydropyran an ideal substrate for in situ oxidative carbon–hydrogen bond cleavage by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in accord with our studies on related transformations.[8] The resulting dihydropyrone can undergo intramolecular nucleophilic addition[9] to yield the target product in which two rings and three bonds are created from readily available precursors.



Scheme 1. Convergent approach to spiroacetal synthesis.

Scheme 2 details the initial demonstration of the process. Condensing the aldehyde **1** with diene **2** (neat) in the presence of Jacobsen's catalyst (**3a**)[10] provided the adduct **4**. Diluting the crude reaction mixture with CH_2Cl_2 followed by adding DDQ yielded **5** nearly instantaneously through carbon–hydrogen bond cleavage and silyl group loss from the intermediate oxocarbenium ion. The sequence was completed by protodesilylation with *p*-TsOH·H_2O to deliver the spiroacetal **6** in 78% yield upon isolated with 91% *ee*. The oxygen atom in the ring appears to be essential for promoting rapid oxidation in consideration of the studies from Guo and Mayr,[11] who showed that carbocyclic enolsilanes add to DDQ rather than form enones.



Scheme 2. One-pot enantioselective cycloaddition/oxidation spiroacetal construction. TBDPS = *tert*-butyldiphenylsilyl.

A brief study on the scope of the process is shown in Table 1. Tetrahydrofuran-containing products can be prepared (entry 1) by shortening the tether between the diene and silyl ether units. Nonfunctionalized aliphatic aldehydes

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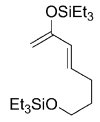
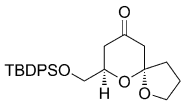
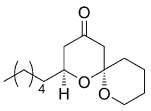
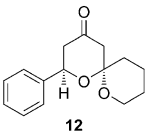
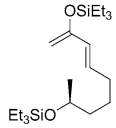
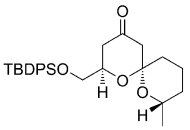
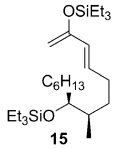
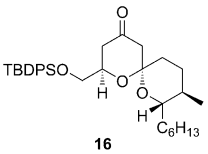
Table 1: Scope exploration.[a]

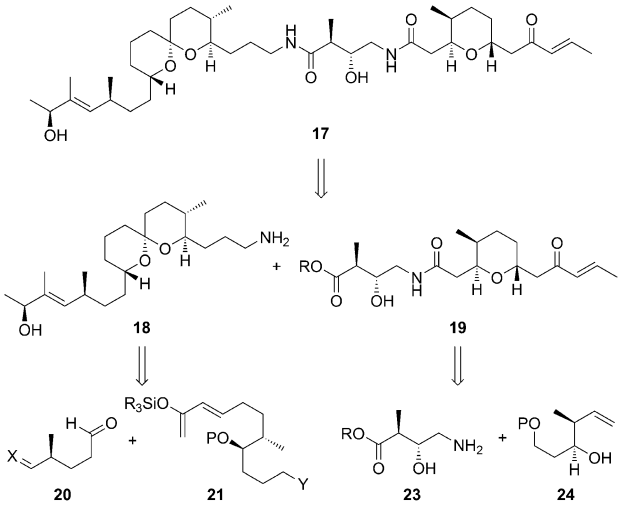
Entry	Diene	Aldehyde	Product	Yield [%][b] (*ee* [%])
1	 **7**	**1**	 **8**	72 (85)
2	**2**	 **9**	 **10**	50 (>99)
3	**2**	 **11**	 **12**	53 (84)
4	 **13**	**1**	 **14**	71 (>99)[c]
5	 **15**	**1**	 **16**	75 (>99)[c]

[a] See the Supporting Information for detailed procedures, substrate syntheses, and stereochemical determination. [b] Yield of isolated, purified product. [c] Diastereomeric products were removed by chromatography.

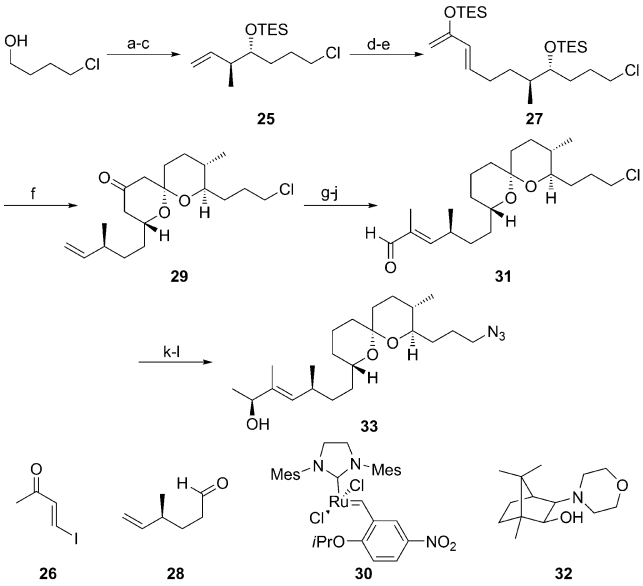
are suitable substrates (entry 2), thus providing the products in excellent enantiomeric purity. Aromatic aldehydes yield aryl-substituted spiroacetals (entry 3). Chiral dienes can be employed in the process (entries 4 and 5). These reactions deliver products as single enantiomers in accord with the Horeau principle.[12] The molecular complexity of the targets in these examples suggests that this strategy is viable for late-stage fragment-coupling syntheses of spiroacetal-containing natural products.

The total synthesis of the sponge-derived cytotoxin bistramide A (**17**; Scheme 3)[13] was initiated to illustrate the merits of this protocol. The structure of bistramide A was confirmed through total synthesis by the group of Kozmin.[14] Several total and partial syntheses of **17** and related structures subsequently appeared.[15] Crystallographic studies[16] showed that interactions between actin (the biological target)[17] and **17** are dominated by the spiroacetal subunit, thus leading to rational analogue designs.[18]

We envisioned bistramide A to arise from the fragments **18** and **19** through amide bond formation. The core spiroacetal unit of **18** will be formed from the cycloaddition/oxidative cyclization between the aldehyde **20** and diene **21**. The righthand fragment can result from the union of the amine **23** and a tetrahydropyran-contaning carboxylic acid derived from the alcohol **24**.



Scheme 3. Retrosynthetic analysis of bistramide A. PG = protecting group.

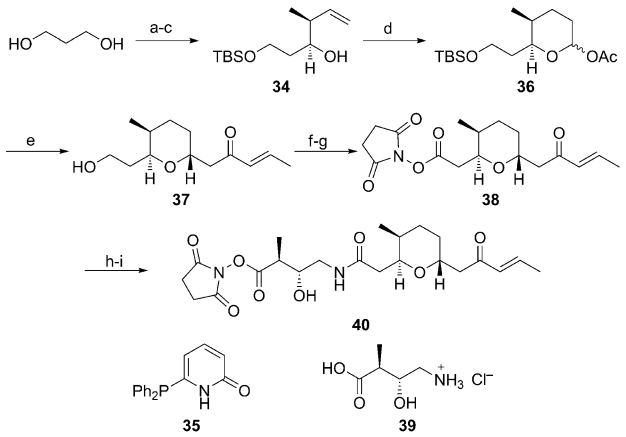


Scheme 4. Synthesis of the spiroacetal subunit. Reagents and conditions: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 83 %; b) *trans*-2-butene, *n*BuLi, KO*t*Bu, (−)-$(Ipc)_2BOMe$, THF, then $BF_3{\cdot}OEt_2$; then aldehyde, −78 °C to RT, 67 %, 90 % *ee*; c) TESCl, imidazole, CH_2Cl_2, quantitative; d) $(9\text{-BBN})_2$, THF, 0 °C to RT; then **26**, $[Pd(dppf)Cl_2]$, K_3PO_4, H_2O, CH_2Cl_2, 73 %; e) TESOTf, Et_3N, CH_2Cl_2, 0 °C, 96 %; f) **28**, **3 b**, 4 Å M.S., then DDQ, CH_2Cl_2; then *p*-TsOH·H_2O, 58 %; g) *p*-$TsNHNH_2$, MeOH; h) $NaBH_3CN$, THF, MeOH, pH > 4, 0 °C; i) NaOAc, EtOH, 75 °C, 54 % (three steps); j) methacrolein, **30**, CH_2Cl_2, 40 °C, 68 %; k) Me_2Zn, **32**, hexanes, 86 %; l) NaN_3, DMF, 60 °C, quantitative. BBN = borabicyclononane, dppf = diphenylphosphinoferrocene, Ipc = isopinocamphenyl, OTf = trifluoromethanesulfonate, Mes = 2,4,6-trimethylphenyl, M.S. = molecular sieves, TES = triethylsilyl, THF = tetrahydrofuran, Ts = toluenesulfonyl.

Our approach to the spiroacetal subunit (Scheme 4) commenced with the oxidation, Brown crotylation,[19] and silylation of 4-choloro-1-butanol to yield **25**. Suzuki coupling[20] with the iodo enone **26**[21] yielded a ketone which was

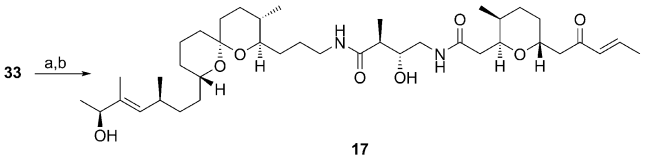
converted into the silyloxy diene **27** under standard reaction conditions. The spiroacetal was constructed by coupling **27** with the aldehyde **28**, which can be accessed in one step from (+)-β-citronellene,[22] in the presence of *ent*-**3b**. DDQ treatment and acid-mediated ring closure yielded the spirocycle **29** in 58% yield as a single stereoisomer. Ketone deoxygenation through a mild variant of the Wolff–Kishner reduction[23] and cross-metathesis with methacrolein mediated by the Grela–Grubbs catalyst (**30**)[24] provided the aldehyde **31**. A diastereoselective addition of Me_2Zn in the presence of (−)-MIB (**32**)[25] and the conversion of the chloride into an azido group completed the synthesis of the spiroacetal subunit **33** as a single stereoisomer within the limits of NMR detection.

We prepared the 2,6-*trans*-tetrahydropyran in the right fragment through homoallylic alcohol hydroformylation, oxocarbenium ion formation, and nucleophilic addition (Scheme 5).[26] Conversion of 1,3-propanediol into the homo-



Scheme 5. Synthesis of the right-hand fragment. Reagents and conditions: a) TBSCl, imidazole, THF, 95%; b) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, 88%; c) *cis*-2-butene, *n*BuLi, KO*t*Bu, (+)-$(Ipc)_2$BOMe, THF, then BF_3·OEt_2; then aldehyde, −78 °C to RT, 67%, 90% *ee*; d) $[Rh(CO)_2acac]$, **35**, H_2/CO (1:1, 8 atm); then Ac_2O Et_3N, DMAP, 91%; e) (*E*)-3-penten-2-one, TMSOTf, Et_3N, CH_2Cl_2, −78 °C, 57%; f) H_5IO_6, CrO_3, CH_3CN, H_2O, 0 °C; g) *N*-hydroxysuccinimide, DCC, CH_3CN, 81% (two steps); h) **39**, *i*Pr_2NEt, DMF; i) *N*-Hydroxysuccinimide, DCC, CH_3CN, 50% (two steps). acac = acetylacetonate, DCC = dicyclohexyl carbodiimide, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, Py = pyridine, TMS = trimethylsilyl.

allylic alcohol **34** proceeded through selective monosilylation, oxidation, and asymmetric crotylation. Hydroformylation was achieved through rhodium catalysis in the presence of Breit's exceptional DPPon ligand (**35**).[27] The resultant lactol was converted into an acetate group in situ to yield **36** in 91% overall yield. The addition of (*E*)-3-penten-2-one to **36** in the presence of TMSOTf[15b,d] provided **37**, with concomitant cleavage of the silyl ether through an acidic work-up. Oxidizing the primary alcohol into a carboxylic acid was achieved through CrO_3 and H_5IO_6. The crude acid was converted into the activated ester **38** with *N*-hydroxysuccinimide and DCC. Coupling **38** with the known β-amino acid



Scheme 6. Completion of the synthesis. Reagents and conditions: a) PMe_3, THF, H_2O; b) **40**, DMF, 69% (two steps).

39[14] provided an amide which was transformed into the activated ester **40** without purification.

The synthesis was completed (Scheme 6) by reducing **33** with PMe_3 in aqueous THF. The crude amine mixture was combined with **40** to provide bistramide A in 69% yield. The longest linear sequence in this route is 14 steps from commercially available starting materials, thus making this the shortest reported synthesis of this natural product (the shortest previous synthesis took 17 steps from commercially available materials). Significantly, this strategy results in a substantial reduction in the overall step count in comparison to published sequences to this family of molecules.

We have demonstrated that the benefits of fragment-coupling asymmetric cycloaddition reactions can be merged with the complexity-increasing capabilities of oxidative carbon–hydrogen bond cleavage for a convergent synthesis of spiroacetals. The substrates are easily prepared, functional-group tolerance is high, and stereocontrol is excellent, thus indicating that this protocol will be applicable to natural product synthesis. The rapid complexity that this sequence provides was exploited in the shortest reported synthesis of the actin-binding cytotoxin bistramide A.

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Communications

Natural Product Synthesis

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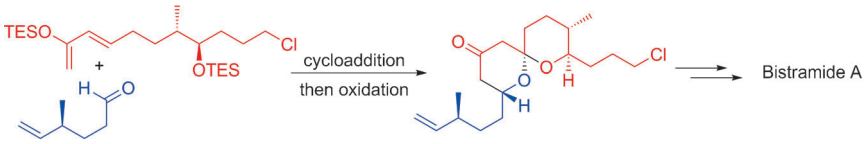
Spiroacetal Formation through Telescoped Cycloaddition and Carbon–Hydrogen Bond Functionalization: Total Synthesis of Bistramide A



Actin' out: Spiroacetals can be prepared from aldehydes and functionalized dienes through a convergent, telescoped sequence of cycloaddition, oxidative C–H bond cleavage, and acid treatment. The functional-group tolerance and facile accessibility of the components render this protocol suitable for the synthesis of structurally complex natural products such as the actin-binding cytotoxin bistramide A.