Published in final edited form as:

Angew Chem Int Ed Engl. 2014 October 6; 53(41): 11075–11078. doi:10.1002/anie.201406819.

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

Xun Han and Prof. Paul E. Floreancig*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260 (USA)

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 that 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.

Keywords

cycloaddition; C–H activation; spiro compound; natural products; stereoselectivity

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 comprised of 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 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 2 details the initial demonstration of the process. Condensing aldehyde **1** with diene **2** (neat) in the presence of Jacobsen's catalyst (**3a**)^[10] provided adduct **4**. Diluting the crude mixture with CH₂Cl₂ 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•H₂O to deliver spiroacetal **6** in 78% isolated yield and 91% ee. The oxygen in the ring appears to be essential for promoting rapid oxidation in consideration of Mayr's studies^[11] showing that carbocyclic enolsilanes add to DDQ rather than form enones.

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. Non-functionalized aliphatic aldehydes are suitable substrates (entry 2), 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 Kozmin group.^[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, leading to rational analog designs.^[18]

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

Our approach to the spiroacetal subunit (Scheme 4) commenced with the oxidation, Brown crotylation,^[19] and silylation of 4-chloro-1-butanol to yield **25**. Suzuki coupling^[20] with iodo enone **26**^[21] yielded a ketone that was converted to silyloxy diene **27** under standard conditions. The spiroacetal was constructed by coupling **27** with aldehyde **28**, which can be accessed in one step from (+)-β-citronellene,^[22] in the presence of *ent*-**3b** (the enantiomer of **3b**). DDQ treatment and acid-mediated ring closure yielded 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 Grell-Grubbs catalyst (**30**)^[24] provided aldehyde **31**. A diastereoselective addition of Me₂Zn in the presence of (–)-MIB (**32**)^[25] and the conversion of the chloride to an azido group completed the synthesis of 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.^[26] The route is shown in Scheme 5. Conversion of 1,3-propanediol to homoallylic 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 to 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 to a carboxylic acid was achieved through CrO₃ and H₅IO₆. The crude acid was converted to activated ester **38** with *N*-hydroxysuccinimide and DCC. Coupling **38** with known β -amino acid **39**^[14] provided an amide that was transformed to activated ester **40** without purification.

The synthesis was completed (Scheme 6) by reducing azide **33** with PMe₃ in aqueous THF. The crude amine was mixed with **40** to provide bistramide A in 69% yield. The longest linear sequence in this route is 14 steps from commercially available starting materials, 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, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- [1]. a) Hendrickson JB. J. Am. Chem. Soc. 1975; 97:5784. b) Wender PA, Verma VA, Paxton TJ, Pillow TH. Acc. Chem. Res. 2008; 41:40. [PubMed: 18159936] c) Newhouse T, Baran PS, Hoffmann RW. Chem. Soc. Rev. 2009; 38:3010. [PubMed: 19847337] d) Gaich T, Baran PS. J. Org. Chem. 2010; 75:4657. [PubMed: 20540516]
- [2]. For reviews, see: Pellissier H. Tetrahedron. 2009; 65:2839. Danishefsky SJ. Aldrichimica Acta. 1986; 19:59.
- [3]. a) Gutekunst WR, Baran PS. Chem. Soc. Rev. 2011; 40:1976. [PubMed: 21298176] b) Brückl T, Baxter RD, Ishihara Y, Baran PS. Acc. Chem. Res. 2012; 45:826. [PubMed: 22017496] c) Yamaguchi J, Yamaguchi AD, Itami K. Angew. Chem. 2012; 124:9092. Angew. Chem., Int. Ed. 2012; 51:8960. d) Chen DY-K, Youn SW. Chem. Eur. J. 2012; 18:9452. [PubMed: 22736530]
- [4]. a) Francke W, Kitching W. Curr. Org. Chem. 2001; 5:233. b) Jacobs MF, Kitching W. Curr. Org. Chem. 1998; 2:395.

- [5]. a) Palmes JA, Aponick A. *Synthesis*. 2012; 44:3699. b) Raju BR, Saikia AK. *Molecules*. 2008; 13:1942. [PubMed: 18794795] c) Aho JE, Pihko PM, Rissa TK. *Chem. Rev.* 2005; 105:4406. [PubMed: 16351049] d) Mead KT, Brewer BN. *Curr. Org. Chem.* 2003; 7:227.
- [6]. a) Danishefsky SJ, Pearson WH. *J. Org. Chem.* 1983; 48:3865. b) Danishefsky SJ, Armistead DM, Wincott FE, Selnick HG, Hungate R. *J. Am. Chem. Soc.* 1989; 111:2976.
- [7]. For reviews of oxidative and cycloaddition-based approaches to spiroacetals, see: Sperry J, Liu Y-C, Brimble MA. *Org. Biomol. Chem.* 2010; 8:29. [PubMed: 20024126] Rizzacasa MA, Pollex A. *Org. Biomol. Chem.* 2009; 7:1053. [PubMed: 19262920]
- [8]. a) Peh GR, Floreancig PE. *Org. Lett.* 2012; 14:5614. [PubMed: 23095114] b) Han X, Floreancig PE. *Org. Lett.* 2012; 14:3808. [PubMed: 22783950] c) Cui Y, Floreancig PE. *Org. Lett.* 2012; 14:1720. [PubMed: 22420412] d) Brizgys GJ, Jung HH, Floreancig PE. *Chem. Sci.* 2012; 3:438. e) Jung HH, Floreancig PE. *Tetrahedron*. 2009; 65:10830. [PubMed: 20640173] f) Liu L, Floreancig PE. *Org. Lett.* 2009; 11:3152. [PubMed: 19552390] g) Liu L, Floreancig PE. *Angew. Chem.* 2010; 122:6030. *Angew. Chem. Int. Ed.* 2010; 49:5894. h) Liu L, Floreancig PE. *Angew. Chem.* 2010; 122:3133. *Angew. Chem. Int. Ed.* 2010; 49:3069. i) Tu W, Floreancig PE. *Angew. Chem.* 2009; 121:4627. *Angew. Chem. Int. Ed.* 2009; 48:4567. j) Tu W, Liu L, Floreancig PE. *Angew. Chem.* 2008; 120:4252. *Angew. Chem. Int. Ed.* 2008; 47:4184.
- [9]. For another example of spiroacetal formation through a formal hydride loss from an oxacycle, see: Donohoe TJ, Lipinski RM. *Angew. Chem.* 2013; 125:2551. *Angew. Chem. Int. Ed.* 2013; 52:2491.
- [10]. Dossetter AG, Jamison TF, Jacobsen EN. *Angew. Chem.* 1999; 111:2549. *Angew. Chem. Int. Ed.* 1999; 38:2398.
- [11]. Guo X, Mayr H. *J. Am. Chem. Soc.* 2013; 135:12377. [PubMed: 23937562] for related earlier studies, see: Ryu I, Murai S, Hatayama Y, Sonoda N. *Tetrahedron Lett.* 1978; 19:3455. Bhattacharya A, DiMichele LM, Dolling U-H, Grabowski EJJ, Grenda VJ. *J. Org. Chem.* 1989; 54:6118. Hodgson DM, Moreno-Clavijo E, Day SE, Man S. *Org. Biomol. Chem.* 2013; 11:5362. [PubMed: 23846424]
- [12]. The Horeau principle describes the statistical enantiomeric excess enhancement when two enantiomerically enriched species are coupled due to diastereomer formation. For a review see: Rautenstrauch V. *Bull. Chem. Soc. Fr.* 1994; 131:515.
- [13]. a) Gouiffès D, Moreau S, Helbecque N, Berrier JL, Hénichart JP, Barbin Y, Laurent D, Verbist JF. *Tetrahedron*. 1988; 44:451. b) Griffiths G, Garrone B, Deacon E, Owen P, Pongracz J, Mead G, Bradwell A, Watters D, Lord J. *Biochem. Biophys. Res. Commun.* 1996; 222:802. [PubMed: 8651926] c) Foster MP, Mayne CL, Dunkel R, Pugmire RJ, Grant DM, Kornprobst JM, Verbist JF, Biard JF, Ireland CM. *J. Am. Chem. Soc.* 1992; 114:1110.
- [14]. Statsuk AV, Liu D, Kozmin SA. *J. Am. Chem. Soc.* 2004; 126:9546. [PubMed: 15291551]
- [15]. a) Wipf P, Hopkins TD. *Chem. Commun.* 2005:3421. b) Crimmins MT, DeBaille AC. *J. Am. Chem. Soc.* 2006; 128:4936. [PubMed: 16608311] c) Lowe JT, Wrona IE, Panek JS. *Org. Lett.* 2007; 9:327. [PubMed: 17217296] d) Yadav JS, Chetia L. *Org. Lett.* 2007; 9:4587. [PubMed: 17918952] e) Tomas L, af Gennäs GB, Hiebel MA, Hampson P, Gueyrard D, Pelotier B, Yli-Kauhialuoma J, Piva O, Lord JM, Goekjian PG. *Chem. Eur. J.* 2012; 18:7452. [PubMed: 22539235] f) Commandeur M, Commandeur C, Cossy J. *Org. Lett.* 2011; 13:6018. [PubMed: 22003969]
- [16]. Rizvi SA, Tereshko V, Kossiakoff AA, Kozmin SA. *J. Am. Chem. Soc.* 2006; 128:3882. [PubMed: 16551075]
- [17]. a) Statsuk AV, Bai R, Baryza JL, Verma VA, Hamel E, Wender PA, Kozmin SA. *Nature Chem. Biol.* 2005; 1:383. [PubMed: 16372404] b) Rizvi SA, Courson DS, Keller VA, Rock RS, Kozmin SA. *Proc. Natl. Acad. Sci. USA.* 2008; 105:4088. [PubMed: 18334642]
- [18]. Rizvi SA, Liu S, Chen Z, Skau C, Pytynia M, Kovar DR, Chmura SJ, Kozmin SA. *J. Am. Chem. Soc.* 2010; 132:7288. [PubMed: 20455580]
- [19]. Brown HC, Bhat KS. *J. Am. Chem. Soc.* 1986; 108:293.
- [20]. Miyaura N, Ishiyama T, Sasaki H, Ishikawa M, Satoh M, Suzuki A. *J. Am. Chem. Soc.* 1989; 111:314.
- [21]. Rivero MR, Buchwald SL. *Org. Lett.* 2007; 9:973–976. [PubMed: 17311390]

- [22]. Fürstner A, Feyen F, Prinz H, Waldmann H. *Angew. Chem.* 2003; 115:5519. *Angew. Chem. Int. Ed.* 2003; 42:5361.
- [23]. Nair V, Sinhababu A. *J. Org. Chem.* 1978; 43:5013.
- [24]. Grela K, Harutyunyan S, Michrowska A. *Angew. Chem.* 2002; 114:4210. *Angew. Chem. Int. Ed.* 2002; 41:4038.
- [25]. Nugent WA. *Chem. Commun.* 1999:1369.
- [26]. Jung HH, Seiders JR II, Floreancig PE. *Angew. Chem.* 2007; 119:8616. *Angew. Chem. Int. Ed.* 2007; 46:8464.
- [27]. a) Breit B, Seiche W. *J. Am. Chem. Soc.* 2003; 125:6608. [PubMed: 12769551] b) Gellrich U, Seiche W, Keller M, Breit B. *Angew. Chem.* 2012; 124:11195. *Angew. Chem. Int. Ed.* 2012; 51:11033.

Scheme 1.
Convergent approach to spiroacetal synthesis.

Scheme 2.

One pot enantioselective cycloaddition/oxidation spiroacetal construction. TBDPS = *tert*-Butyl diphenylsilyl.

Scheme 3.
Retrosynthetic analysis of bistramide A.

Scheme 4.

Synthesis of the spiroacetal subunit. Reagents and conditions: a) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78°C , 83%; b) *trans*-2-Butene, $n\text{BuLi}$, $\text{KO}t\text{Bu}$, $(-)\text{-(Ipc)}_2\text{BOMe}$, THF, then $\text{BF}_3\cdot\text{OEt}_2$, 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**, **3b**, 4 Å MS, then DDQ, CH_2Cl_2 , then *p*- $\text{TsOH}\cdot\text{H}_2\text{O}$, 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**, hexane, 86%; l) NaN_3 , DMF, 60°C , quantitative. TES = triethylsilyl, Mes = 2,4,6-trimethylphenyl, Ipc = isopinocampheyl, BBN = borabicyclononane, dppf = diphenylphosphino-ferrocene, OTf = trifluoromethanesulfonate, Ts = toluenesulfonyl.

Scheme 5.

Synthesis of the right-hand fragment. Reagents and conditions: a) TBSCl, imidazole, THF, 95%; b) $\text{SO}_3 \cdot \text{Py}$, DMSO, Et_3N , CH_2Cl_2 , 88%; c) *cis*-2-Butene, *n*BuLi, KO*t*Bu, (+)-(Ipc)₂BOMe, THF, then $\text{BF}_3 \cdot \text{OEt}_2$, then aldehyde, -78°C to rt, 67%, 90% ee; d) $\text{Rh}(\text{CO})_2\text{acac}$, **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*Pr₂NEt, DMF; i) *N*-Hydroxysuccinimide, DCC, CH_3CN , 50% (two steps). Py = pyridine, acac = acetylacetonate, DMAP = 4-dimethylaminopyridine, DCC = dicyclohexyl carbodiimide.

Scheme 6.

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

Table 1

Scope exploration.^[a]

entry	diene	aldehyde	product	yield ^[b] (ee)
1				72% (85%)
2				50 (>99%)
3				53 (84%)
4				71 (>99%) ^[c]
5				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.