

Multicomponent Linchpin Couplings of Silyl Dithianes via Solvent-Controlled Brook Rearrangement

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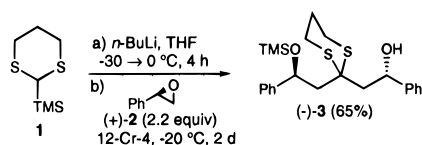
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We and others have extensively employed dithiane couplings^{1,2} with epoxides, α -alkoxy iodides and tosylates, and aldehydes for the stereocontrolled generation of protected aldol linkages and the union of advanced fragments in complex molecule synthesis.^{3,4} Recent studies have also established the tactical advantages of domino reactions⁵ and two-direction chain extension.⁶ Herein we report the one-flask linchpin coupling of 2-(trialkylsilyl)-1,3-dithiane with two different electrophiles via solvent-controlled Brook rearrangement.⁷

In 1994 Tietze and co-workers described⁸ the symmetrical bisalkylation of trimethylsilyldithiane (**1**) with 2 equiv of a scalemic epoxide [e.g., (+)-**2**, Scheme 1]. Following initial reaction of the lithio derivative of **1** with the epoxide, the resultant alkoxide undergoes 1,4-Brook rearrangement,⁷ transferring the silyl group to oxygen and generating the 2-alkyl lithiated dithiane; coupling with a second molecule of the epoxide then yields (–)-**3**. This process requires a reaction time of 2 days and is inapplicable to unsymmetrical couplings (vide infra).

Scheme 1



(1) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075.
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(5) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (d) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.

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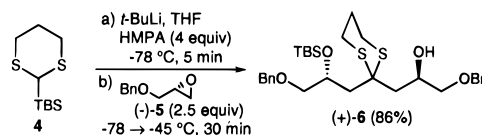
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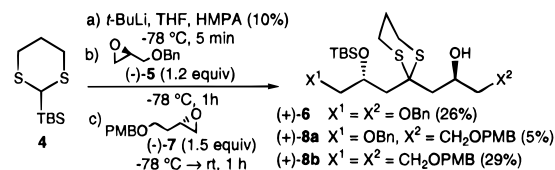
In our syntheses of FK506,^{3a} rapamycin and demethoxyrapamycin,^{3b} and discodermolide,^{3c} treatment with *t*-BuLi in 10% HMPA/THF at -78 °C proved to be the optimum protocol⁹ for rapid generation of 2-substituted dithiane anions.¹⁰ We began the present study by using these conditions for bisalkylation of 2-*tert*-(butyldimethylsilyl)-1,3-dithiane (**4**),¹¹ a substrate also successfully employed by Tietze which leads to installation of the more robust TBS hydroxyl protecting group. Metalation of **4** in 10% HMPA/THF and immediate addition of epoxide (–)-**5** readily afforded (+)-**6** in good yield (Scheme 2).¹²

Scheme 2



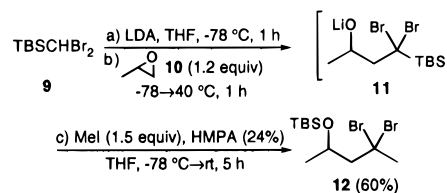
In the presence of HMPA, both the initial alkylation of **4** and the subsequent Brook rearrangement occur within minutes at -78 °C. Accordingly, the attempted sequential reaction of **4** with epoxides (–)-**5** and (–)-**7** led to a mixture of symmetrical and unsymmetrical products [(+)-**6**, (+)-**8a**, and (+)-**8b**, Scheme 3]. This result suggested that linchpin coupling of different electrophiles would be feasible only if the Brook rearrangement could be suppressed until the first alkylation was complete.

Scheme 3



Fortuitously, an elegant recent study by Oshima, Utimoto, and co-workers revealed dramatic solvent effects on similar Brook rearrangements in the adducts of lithio dihalo(trialkylsilyl)methanes with epoxides (Scheme 4).¹³ Rearrangement did not occur following metalation and initial alkylation in THF but proceeded readily upon addition of HMPA; the resultant

Scheme 4



(10) For an insightful discussion of the ion-pair solution structures of 2-lithio-1,3-dithianes in THF and HMPA/THF, see: Reich, H. J.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869.

(11) We prepared **4** in multigram quantities by addition of *tert*-butyldimethylchlorosilane to the lithio derivative of 1,3-dithiane in THF at -78 °C \rightarrow room temperature over 2 h.

(12) All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ¹H NMR, and 125-MHz ¹³C NMR spectra as well as appropriate parent ion identification by high resolution mass spectrometry.

(13) (a) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503. (b) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1993**, *34*, 1951.

(14) Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. I* **1979**, 26.

(15) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

(16) HMPA appears to be more effective than DMFU.

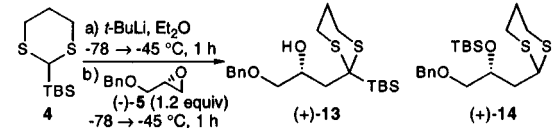
(17) In preliminary studies, 2-(trimethylsilyl)- and 2-(triethylsilyl)-1,3-dithiane afforded lower yields of coupling products.

(18) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302.

O-silyl organolithium could then react with a second electrophile. The analogous unsymmetrical bisalkylation of TM-SCHLiCN with two epoxides in DME has also been reported,¹⁴ although in this case it is unclear how the timing of the Brook rearrangement was controlled.

Metalation of **4** and alkylation with epoxide (–)-**5** in Et₂O or THF likewise furnished the unrearranged carbinol (+)-**13** exclusively (Table 1, entries 1 and 2). In contrast, addition of HMPA or DMPU^{15,16} (entries 3 and 4) induced the 1,4-Brook rearrangement, affording predominantly silyl ether (+)-**14**.

Table 1. Solvent Effects on Brook Rearrangement in Coupling of Silyl Dithiane **4** with Epoxide (–)-**5**



Entry	Solvent	Additive ^a	Yield 13 (%)	Yield 14 (%)
1	THF	-	60	-
2	Et ₂ O	-	74	-
3	Et ₂ O	HMPA	9	56
4	Et ₂ O	DMPU	12	66

^a Following step b, the reaction mixture was cooled to –78 °C, treated with 0.3–0.4 equiv of additive in Et₂O, and warmed to –45 °C for 1 h.

Encouraged by these results, we reinvestigated the one-pot linchpin coupling of dithiane **4** with two different electrophiles. Following deprotonation and addition of epoxide (–)-**5** in Et₂O, introduction of HMPA plus a second epoxide or benzyl bromide afforded the unsymmetrical bisalkylated products in 56–74% yields (Table 2).¹⁷ Scalemic epoxides are particularly well suited to this process, because the configurations of the resulting carbinol stereocenters are predetermined, circumventing the formation and separation of unwanted diastereomers. Previous studies of 2-lithio-2-alkyldithianes suggest that a variety of other electrophiles should also be accommodated in the second step.² Importantly, the substituents in several adducts (e.g., epoxides **22** and **24**) are poised for further elaboration.

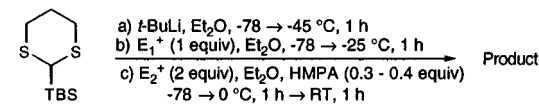
We have utilized the one-step coupling protocol to link advanced intermediates in several of our ongoing synthetic programs. For example, sequential alkylations of dithiane **4** with epoxides (+)-**25** and (–)-**26** gave exclusively the spongistatin¹⁸ fragment (+)-**27** in 59% yield (Table 2, entry 6). A survey of the literature suggests that the new protocol should prove applicable to nearly all total syntheses utilizing dithiane coupling strategies.

We have further extended this methodology by assembling a *five-component* coupling product in a single operation. Following alkylation of dithiane **4** with epoxide (–)-**5** (2.6 equiv each) to generate the unrearranged alkoxy dithiane **28**, sequential addition of HMPA and (–)-epichlorohydrin (**21**, 1 equiv) furnished the bis(silyloxy dithiane) carbinol (+)-**29** in 66% yield, accompanied by a minor amount (ca. 2%) of epoxide (+)-**22** (Scheme 5). This new strategy, if general, should result in exceptionally concise routes to complex 1,3-polyol natural products, including polyene macrocycles and macrolides such as roflamycoin (**30**).¹⁹

The further development of one-step linchpin couplings of silyl dithianes and applications to natural product synthesis are currently under active investigation.

(19) (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (b) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635.

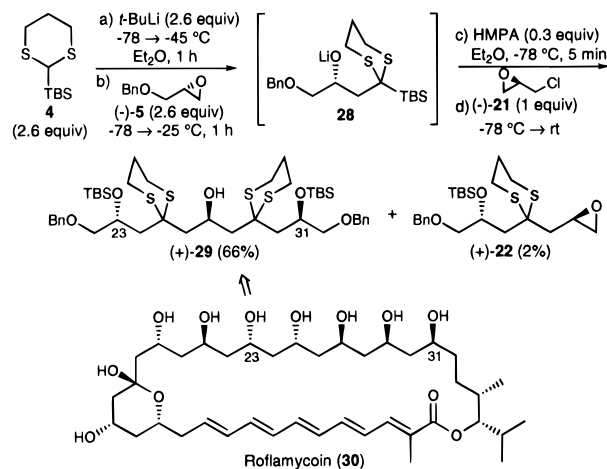
Table 2. Unsymmetrical Linchpin Couplings of Silyl Dithiane **4**



Entry	E ₁ ⁺	E ₂ ⁺	Product	Yield (%) ^b
1	BnO-CH ₂ -CH ₂ -epoxide (–)- 5	OTBS-CH ₂ -CH ₂ -epoxide (–)- 15	BnO-CH ₂ -CH ₂ -CH(OH)-CH ₂ -CH ₂ -OTBS (+)- 16	56
2	BnO-CH ₂ -CH ₂ -epoxide (–)- 5	OTBS-CH ₂ -CH ₂ -epoxide (–)- 17	BnO-CH ₂ -CH ₂ -CH(OH)-CH ₂ -CH ₂ -OTBS (+)- 18	74
3	BnO-CH ₂ -CH ₂ -epoxide (–)- 5	Br-CH ₂ -Ph 19	BnO-CH ₂ -CH ₂ -CH(OH)-CH ₂ -CH ₂ -Ph (+)- 20	62
4 ^a	BnO-CH ₂ -CH ₂ -epoxide (–)- 5	OTBS-CH ₂ -CH ₂ -epoxide (–)- 21	BnO-CH ₂ -CH ₂ -CH(OH)-CH ₂ -CH ₂ -epoxide (+)- 22	60
5 ^a	BnO-CH ₂ -CH ₂ -epoxide (–)- 5	OTBS-CH ₂ -CH ₂ -epoxide (+)- 23	BnO-CH ₂ -CH ₂ -CH(OH)-CH ₂ -CH ₂ -epoxide (+)- 24	71
6	OTBS-CH ₂ -CH ₂ -epoxide (+)- 25	OTBS-CH ₂ -CH ₂ -epoxide (–)- 26	OTBS-CH ₂ -CH ₂ -CH(OH)-CH ₂ -CH ₂ -ODMB (+)- 27	59

^a Only 1 equiv of E₂⁺ was used. ^b After chromatography.

Scheme 5



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Supporting Information Available: Characterization data for compounds **4**, **6**, **8a**, **8b**, **13**, **14**, **16**, **18**, **20**, **22**, **24**, **27**, and **29** (6 pages). See any current masthead page for ordering and Internet access instructions.

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