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Efficient access to 2,5-substituted tetrahydrofurans via a one-pot cyclization of di- and triepoxides

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ABSTRACT

The one-pot addition and cyclization of 1,5-diepoxyhexane with a range of organolithium species provides efficient access to 2,5-substituted tetrahydrofurans (THFs), common structural motifs found in a range of natural products and pharmaceutical ingredients. Extension of this reaction to triepoxides has also been demonstrated to access adjacently linked bis-THF motifs in a single step.

Substituted tetrahydrofuran (THF) ring systems are common structural motifs found in a wide variety of natural product families. From a biosynthetic perspective,[1] their formation arises from the isomerization of intermediate hydroxy epoxide precursors in secondary metabolites such as the marine macrolide amphidinolide E (**1**, Fig. 1)[2] and the bis-THF acetogenin rollidecin C (**2**).[3] The wide variety of biologically active THF-containing natural products have also inspired the pharmaceutical sector to incorporate this privileged structural motif in potential drug candidates. For instance Uriach Pharma have prepared a range of 2,5-substituted THFs,[4] such as **3**, which display platelet aggregation factor activity. Due to the importance of these frameworks, they have been the target of considerable synthetic studies giving rise to numerous and elegant methodologies for their preparation.[5] However, the potential of directly accessing the 2,5-substituted THF motif from the controlled opening of 1,5-diepoxyhexanes remains a relatively unexplored synthetic tactic. In 1950, Wiggins and Wood reported the cyclization of 1,5-diepoxyhexane under methanolysis or aminolysis conditions to give the tetrahydrofuran and piperidine products, respectively.[6] The latter has seen application in the synthesis of azasugar derivatives.[7] In contrast, the addition of carbon-based nucleophiles has garnered limited attention, apart from the 2001 report by Le Merrer and co-workers,[8] where a range of C-aryl-arabinose analogs were prepared by the addition of aryllithium derivatives to a Bn-protected D-mannitol-derived diepoxide. However, applications beyond modified carbohydrate motifs remain unexplored, particularly in the context of natural product synthesis, where practical access to such frameworks would be advantageous, building in the THF motif and latent functionality at an early stage with the advantage of minimizing protecting group manipulations.

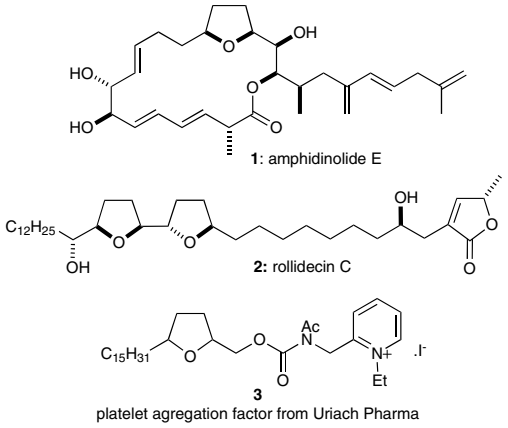

Figure 1. 2,5-Substituted THF motifs in natural products and pharmaceutical agents.

Herein, we report on our work on the development of a one-pot addition and cyclization of 1,5-diepoxyhexane to 2,5-substituted THFs and the extension of this methodology to the synthesis of adjacently linked bis-THF motifs from 1,5,9-triepoxydecane.

We initially focussed our studies on identifying appropriate reaction conditions to affect successful mono-addition followed by 5-*exo* cyclization using *rac/meso* diepoxyhexane **4** (prepared from 1,5-hexadiene by mCPBA epoxidation,[9] 73% yield), as detailed in Table 1. As a benchmark, addition of allyl cuprate to **4**, followed by treatment of the crude monoaddition adduct with K_2CO_3 in MeOH gave the corresponding diastereomeric *syn/anti* THFs **5** and **6** in a moderate 48% yield as an inseparable mixture (entry 1). The major byproduct of the reaction was the corresponding diols resulting from double addition to the diepoxide. In an effort to improve upon this result and facilitate the cyclization of the presumed intermediate epoxy alcohol in situ, $BF_3{\cdot}OEt_2$ was added

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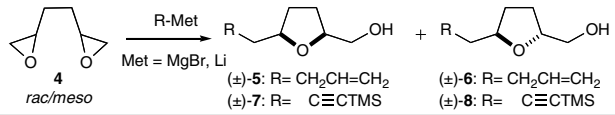
Table 1
Development of reaction conditions using *rac*/*meso* diepoxyhexane **4**



Entry	R–Met	Conditions	Product	Yield[a] (%)
1		(i) CuI,THF,−78 to 0 °C; (ii) K_2CO_3 MeOH	**5** + **6**	48
2		CuI, $BF_3{\cdot}OEt_2$, THF,−78 to 0 °C		—
3		$BF_3{\cdot}OEt_2$, THF,−78 to 40 °C	**7** + **8**	76

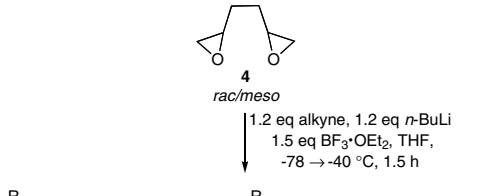
[a] Isolated yield of combined diastereomers after column chromatography.

which led only to decomposition (entry 2). The incompatibility of the organocuprate reagents with Lewis acids led us to return to the use of organolithium species in combination with $BF_3{\cdot}OEt_2$. Thus, addition of the lithium anion of TMS-acetylene (1.2 equiv, from deprotonation with *n*-BuLi) in the presence of $BF_3{\cdot}OEt_2$ (1.5 equiv) to **4** in THF (−78 to −40 °C over 1.5 h) gave the corresponding THFs **7** and **8** in an excellent 76% yield (entry 3).

With optimal conditions developed for the addition and cyclization with TMS-acetylene to *rac/meso* diepoxyhexane **4**, we next investigated the addition of a range of lithium acetylide species, as detailed in Table 2. In all instances (entries 2–5) addition of 1.2 equiv of the lithium acetylide in the presence of $BF_3{\cdot}OEt_2$ to **4** gave the corresponding pairs of diastereomeric THF products **7**–**16** in good to excellent yields (62–80%).[10]

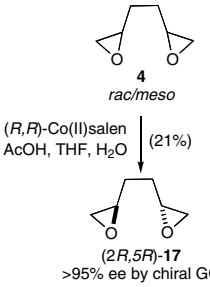
For this one-pot protocol to have utility in the context of complex molecule synthesis, reliable access to the requisite C_2-symmetric diepoxyhexane, in either enantiomeric form, was required.[11] This was conveniently achieved using the Jacobsen hydrolytic kinetic resolution (HKR) reaction,[12] as outlined in Scheme 1. Thus, treatment of *rac/meso* diepoxide **4**, with activated (*R,R*)-Co(III)salen(OAc) complex, using a modification of Jamison's

Table 2
One-pot addition and cyclization with alkynes



Entry	Alkyne	Product	Yield[a] (%)
1		**7** + **8**	76
2		**9** + **10**	73
3		**11** + **12**	65
4		**13** + **14**	62
5		**15** + **16**	80

[a] Combined yield of diastereomers after column chromatography.

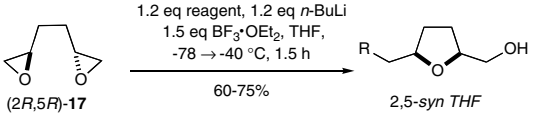


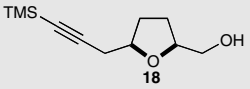
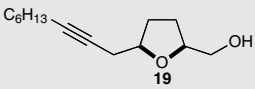
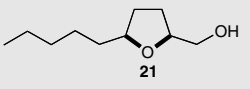
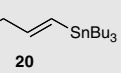
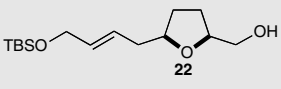
Scheme 1. Preparation of C_2-symmetric 1,5-diepoxyhexane **17.**

HKR conditions, provided (2*R*,5*R*)-diepoxyhexane **17** in 21% yield with >95% ee on multigram scale.[13]

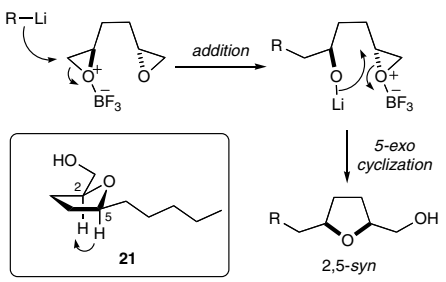
With (2*R*,5*R*)-diepoxyhexane **17** in hand, we turned our attention to its use in the preparation of enantiomerically pure THFs and extending the scope and generality of the addition/cyclization reaction to include alkyl- and vinyllithium species, as detailed in Table 3. Under our optimized conditions, addition of the lithium anions of TMS-acetylene and 1-octyne proceeded smoothly to provide the corresponding 2,5-*syn* THFs **18** and **19** as single diastereomers, respectively (entries 1 and 2).

Table 3
One-pot addition and cyclization of C_2-symmetric diepoxyhexane (2*R*,5*R*)-**17**



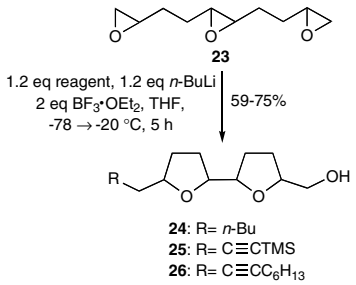
Entry	Reagent	Product	Yield[a] (%)
1		 **18**	75
2		 **19**	65
3	*n*-BuLi	 **21**	62
4	 **20**	 **22**	60

[a] Yield of sole diastereomeric product after column chromatography.



Scheme 2. Confirmation of relative stereochemistry and proposed mechanism.

Table 4
Addition and double cyclization of 1,5,9-triepoxydecane **25**



Entry	Reagent	Product	Yield[a] (%)
1	*n*-BuLi[b]	**24**	70
2	TMS—≡	**25**	75
3	C_6H_{13}—≡	**26**	59

[a] Combined yield of diastereomeric mixtures after column chromatography.
[b] 1.2 equiv of *n*-BuLi was added as the reagent.

Gratifyingly, the addition of both *n*-butyllithium and the lithium species derived from vinylstannane **20**,[14] again proceeded smoothly to provide the corresponding 2,5-*syn* THF products **21** and **22** in good yields (entries 3 and 4).

The 2,5-*syn* relationship in the THF products was confirmed by NOE analysis of **21**, which showed a diagnostic NOE from H2 to H5 (Scheme 2). This observation is consistent with a mechanism whereby Lewis acid activation of either terminal epoxide promotes the 1° opening with the organolithium species, which is then followed by an intramolecular 5-*exo tet* cyclization giving rise to the 2,5-*syn* substitution in the THF products.

In a further extension of the present study, we considered the feasibility of applying the one-pot addition/cyclization conditions to 1,5,9-triepoxydecane **23** (prepared as a mixture of diastereomers from 1,5,9-decatriene by mCPBA epoxidation, 79% yield)[15] to access adjacently linked bis-THFs, as shown in Table 4. Gratifyingly, only slight modifications to our optimized conditions were required in order to obtain the addition/ double cyclization products **24**, **25**, and **26** in excellent yields as diastereomeric mixtures (entries 1–3).

In summary, we have developed and applied a highly efficient one-pot addition cyclization reaction for the synthesis of 2,5-*syn* tetrahydrofurans. This protocol allows rapid access to this privileged motif in a single step from *C*2-symmetric 1,5-diepoxyhexane **17**, and can incorporate a range of functional groups for further elaboration in the context of natural product synthesis. In a further extension, we have shown that adjacently linked bis-THFs can be prepared in a similar manner from 1,5,9-triepoxides. Current studies are focused on the synthetic application of this protocol in the context of the synthesis of amphidinolide E and acetogenins, which will be reported in due course.

Acknowledgments

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10. All new compounds gave spectroscopic data in agreement with assigned structures. A typical procedure for the one-pot cyclization: to a solution of 1-octyne (235 μL, 1.58 mmol) in THF (7 mL) at −78 °C was added *n*-butyllithium 1.6 M in hexane (1.0 mL, 1.60 mmol). After 30 min (2*R*,5*R*)-1,5-diepoxyhexane **17** (150 mg, 1.31 mmol) in THF (3 mL) was added dropwise at −78 °C, followed by the dropwise addition of $BF_3{\cdot}Et_2O$ (240 μL, 1.97 mmol). The mixture was warmed up to −40 °C over 1.5 h and was quenched with NH_4Cl (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL), and the organic phases were combined, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30% EtOAc/hexanes) to give the **19** as a colorless oil (190 mg, 65%). R_f 0.30 (30% EtOAc/hexanes) $[\alpha]_D^{20}$ +20.4 (*c* 1.3, $CHCl_3$); IR (thin film, cm^{-1}) 3394, 2924, 2857, 2212, 1457, 1376, 1046; ^1H NMR (300 MHz, $CDCl_3$) 4.02–3.96 (2H, m), 3.67–3.62 (1H, dd, *J* = 11.6, 3.2 Hz), 3.46–3.40 (1H, dd, *J* = 11.6, 5.1 Hz), 2.65 (1H, br s), 2.37 (2H, dt, *J* = 5.1, 2.7 Hz), 2.08 (1H, tt, *J* = 7.1, 2.4 Hz), 1.97–1.82 (2H, m), 1.80–1.72 (2H, m), 1.44–1.39 (2H, m), 1.32–1.19 (6H, m), 0.82 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 82.4, 80.3, 78.1, 76.4, 65.3, 31.5, 30.6, 29.1, 28.7, 27.3, 25.6, 22.7, 18.9, 14.2; HRMS (ESI) calculated for $C_{14}H_{28}O_2N$ $[M+NH_4]^+$ 242.2115; found: 242.2114.
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