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4-(Phenylsulfonyl)-4-lithiocyclopentene as a nucleophilic 2-pentene-1,5-dial synthetic equivalent. An aziridine-based synthetic approach to (−)-alstonerine

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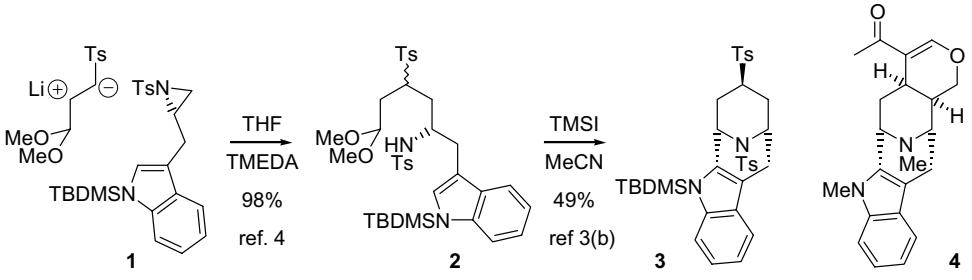
Abstract—Reaction of 4-lithio-4-(phenylsulfonyl)cyclopentene with an L-tryptophan-derived *N*-tosylaziridine provides an adduct. Oxidative cleavage of the cyclopentene double bond provides a dialdehyde, which enters into acid-catalysed Pictet–Spengler-type bicyclisation to give a tetracyclic aldehyde. Completely regioselective silyl dienol ether formation followed by completely stereoselective hetero-Diels–Alder reaction with monomeric formaldehyde gives a late-stage intermediate in a planned total synthesis of the macroline-related alkaloid (−)-alstonerine.

Previous work in this laboratory has been concerned with the use of *N*-substituted aziridines[1] derived from α-aminoacids as building blocks for the assembly of pyrrolidines[2] and piperidines.[3] In the latter context, we demonstrated that aziridine-derived 1,4-bis(tolylsulfonyl)tetrahydropyridines are substrates for highly stereoselective, acid-catalysed reduction and cyclisation processes. We showed further that in some cases the acyclic precursors of bis(tolylsulfonyl)tetrahydropyridines undergo acid-catalysed bicyclisation to give more complex structures directly. Specifically, we found that substrate **2** could readily be made by combining the lithioanion of 1-phenylsulfonyl-3,3-dimethoxypropane with the L-tryptophan-derived aziridine **1**.[4] Subsequent treatment with iodotrimethylsilane (TMSI) provided the indole-containing tetracycle **3** in moderate yield,[3b] avoiding the need to isolate the intermediate tetrahydropyridine (Scheme 1). We became interested in applying this chemistry in a total synthesis of the macroline-related alkaloid (−)-alstonerine **4**,[5] since it was anticipated that a Pictet–Spengler-type[6] acid-mediated cyclisation related to that depicted in Scheme 1 would



Scheme 1.

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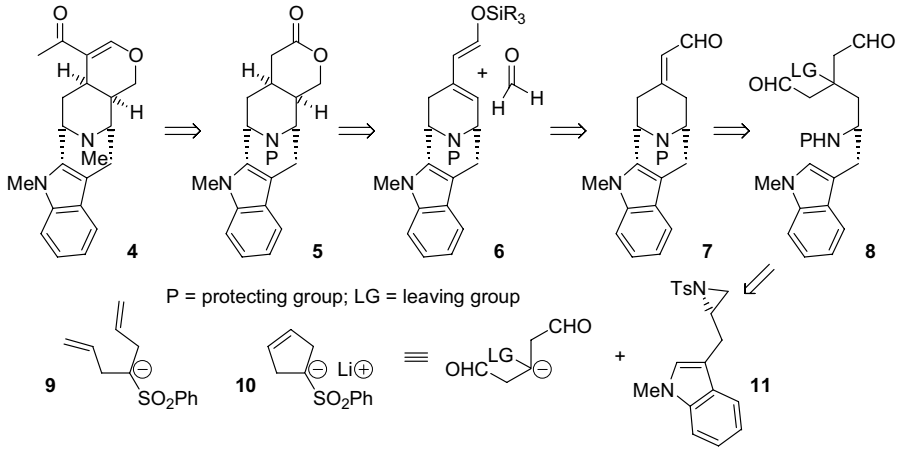


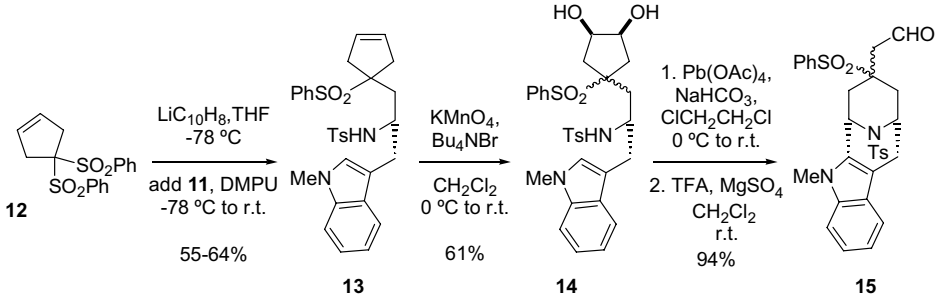
Scheme 2.

allow rapid access to an advanced, tetracyclic intermediate from relatively simple starting materials. This letter reports the results of these investigations.

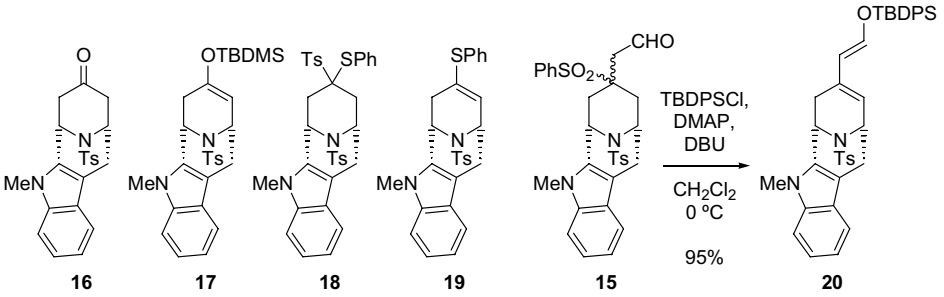
Our retrosynthetic analysis is shown in Scheme 2. We reasoned that the vinylogous ester moiety embedded in the oxygen heterocyclic ring of **4** could be elaborated at a late stage from a δ-lactone **5**. This would be accessed by an unusual hetero-Diels–Alder reaction[7] involving combination of formaldehyde with the silyl dienol ether **6**, which in turn would be generated from the enal **7**. In light of the conversion **2** → **3** depicted in Scheme 1, the identification of enal **7** as a key intermediate target indicated dialdehyde **8** or a derivative as a cyclisation substrate. Pictet–Spengler-type cyclisation and E1cB elimination would provide the enal. Intermediate **8** would be accessed by reaction of the L-tryptophan-derived aziridine **11** with a synthetic equivalent of the 3-pentane-1,5-dial synthon possessing anionic character and a leaving group at C3, followed by unmasking of the aldehyde groups. Our previous success[2,3] in combining sulfone-stabilised carbanions with aziridines in nucleophilic ring-opening reactions led us to focus on sulfone-containing intermediates. It occurred to us that 4-(phenylsulfonyl)-4-lithiocyclopentene **10**[8] possessed both the necessary latent 1,5-dialdehyde in the form of a cyclopentene and the masked double bond inherent in the presence of the sulfone as a potential leaving group. It was felt also that the cyclic nature of the highly substituted anion would maximise its nucleophilicity through minimisation of steric crowding, and this indicated its selection in preference to acyclic congeners such as the 1,6-diene-containing species **9**.

Prior to our work, the studies by Mioskowski had involved the generation of **10** by reductive desulfonylation of 4,4-bis(phenylsulfonyl)cyclopentene **12** using dissolving metal conditions.[8] Thus, treatment of **12**[9] with lithium naphthalenide and addition of aziridine **11**[10] gave the adduct **13** in a maximum yield of 72%, though typically yields were in the range 55–64%. After extensive experimentation, it was found that dihydroxylation of the cyclopentene double bond was best carried out using a modified permanganate reagent system, which provided the *cis*-diols **14** as a 4:1 diastereomeric mixture in ca. 60% yield.[11] Subsequent $Pb(OAc)_4$-mediated oxidative cleavage gave a dialdehyde, which without purification was subjected directly to trifluoroacetic acid-catalysed cyclisation in the presence of rigorously dried $MgSO_4$, providing the tetracycle **15** as a 1:1 epimeric mixture in excellent yield from **14**. The synthesis of key aldehyde **15** is depicted in Scheme 3.

With a short sequence to **15** established, a key issue remained concerning the regiochemistry of dienol ether formation. It was postulated that on exposure to base



Scheme 3.



Scheme 4.

and silylating reagent **15** would suffer E1cB reaction to give an enal, or enals followed by silyl dienol etherification by proton removal from the enal or an *O*-silyl oxonium intermediate. This deprotonation would have to occur with complete selectivity for one of the two γ-positions, irrespective of enal geometry. Our expectation that this would be the case stemmed from an earlier phase of the work, where it had been observed that upon treatment with TBDMSOTf–Et_3N, ketone **16** gave the single regioisomeric enol ether **17**, and that when exposed to $AlCl_3$, thioacetal **18** gave only the vinylsulfide **19**.[12] This striking regioselectivity pointed towards a strong kinetic and/or thermodynamic preference in the deprotonation reactions α- to the piperidine C4 sp^2-hybridised carbon atom in such systems, and we reasoned that the enal vinylogues should show similar behaviour. In the event, exposure of **15** to DBU-TBDPSCl in the presence of sub-stoichiometric DMAP gave in 95% yield the dienol ether **20** as the only detectable isomer (Scheme 4). The identity of **20** followed from ^1H NMR COSY experiments,[13] and from its subsequent behaviour in the hetero-Diels–Alder reactions. The TBDPS containing dienol ether **20** showed markedly better stability than the TBMDS or TIPS derivatives, which were made under analogous conditions in 79% and 47% yields, respectively. The overall yield of **20** over five steps from aziridine **11** and bis(sulfone) **12** was 35%.

Attention was turned finally to the hetero-Diels–Alder reaction of dienol ether **20** with formaldehyde. After numerous attempts failed in achieving cycloaddition using various sources of formaldehyde (paraformaldehyde, 1,3,5-trioxane) in conjunction with a range of Lewis acidic additives ($BF_3{\cdot}OEt_2$, lanthanide triflates, $TiCl_4$, Me_3Al, Me_2AlCl), efforts were focused on use of the monomeric reagent. Eventually, it was found that treatment of **20** with chlorodimethylaluminium and ca. 2 M THF solutions of formaldehyde prepared using a modification of the Schlosser method[14,15] provided the cycloadduct **21** as a single stereoisomer in 36% yield. The structure of **21** was unambiguously established by X-ray crystallographic analysis of the methyl ether derivative **22** (Fig. 1).[16] This demonstrated that cycloaddition had occurred with the desired β-stereoselectivity, and that the structure of **20** was correctly assigned. Cycloadduct **21** was found during NMR studies to be unstable in $CDCl_3$ solution, undergoing retro-cycloaddition with regeneration of **20** and paraformaldehyde with a half-life of ca. 2 h at room temperature (Scheme 5).

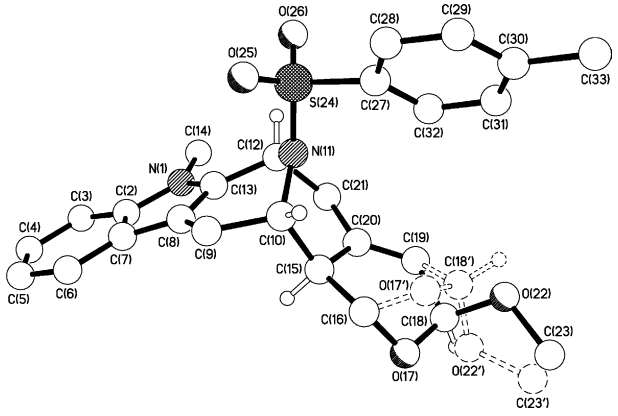
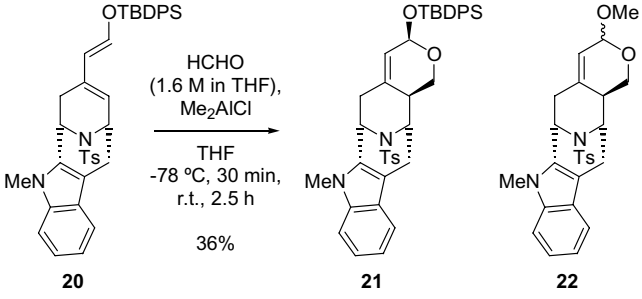


Figure 1. X-ray crystal structure of **22**.



Scheme 5.

In summary, we have achieved the enantiospecific synthesis of a late-stage intermediate for the synthesis of (−)-alstonerine starting from L-tryptophan and 4,4-bis(phenylsulfonyl)cyclopentene. This short sequence clearly establishes the effectiveness of 4-phenylsulfonyl-4-lithiocyclopentene as the synthetic equivalent of a nucleophilic 2-pentene-1,5-dial synthon. In addition, in contrast to existing approaches[5] the Pictet–Spengler reaction achieves the synthesis of both new nitrogen-containing rings in a single transformation. Finally, the route involves an unusual hetero-Diels–Alder reaction of monomeric formaldehyde, and we have uncovered remarkable regioselectivity in some derivatisation reactions of indolo-9-azabicyclo[3.3.1] systems. Further studies will look at the selective hydrogenation of **21** and elaboration of the oxygen heterocycle with a view to completing the total synthesis of (−)-alstonerine.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.033.

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10. Aziridine **11** was synthesised in four steps from commercially available (Aldrich Chemical Co.) 1-methyl-L-tryptophan, by sequential methyl esterification, *N*-tosylation, ester reduction and aziridination (70% overall). Full details are provided in the online Supplementary information.
11. We tentatively assign the major isomer as having the *anti* relationship of the *cis*-diol and the phenylsulfonyl group.
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13. We thank Mr. R. N. Sheppard (Imperial College) for these experiments.
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16. We thank Dr. A. J. P. White (Imperial College) for the X-ray structure determination. Full details will be reported elsewhere.