Tetrahedron Letters, Vol.31, No.28, pp 3965-3968, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SYMMETRY-ENHANCED REMOTE DICARBANION ANNULATIONS FOR LATENT CYCLOALKENONES: APPLICATIONS TO ALKALOIDS AND TERPENES

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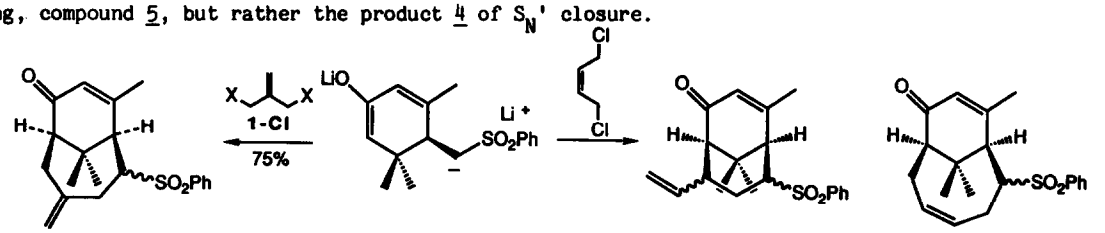
Abstract: Functionalized 1,n-dicarbanions (n=4,5,6) react with α,α'-methallyl dihalides to produce n+3 substituted α-methylenecycloalkanes that are synthetic equivalents of two differentiable cycloalkenones.

Cyclopentenones and cyclohexenones are versatile and easily preparable carbocyclic building blocks in organic synthesis. We have become interested in strategic approaches directly to larger ring cycloalkenone precursors, especially synthetic equivalents that contain two latent α,β-unsaturated ketone units which can be unveiled individually and utilized as needed. Such sequences would be especially valuable for approaching hydroazulenic natural products and those containing 5/8 fused ring systems (cf. 23 → 25 → 27 & 28, Scheme 3). To implement such a strategy, we are investigating tandem reactions of non-equivalent, remote dicarbanions with doubly electrophilic trimethylenemethanes.[1,2]

The structurally-challenging annulation of 1,4-dicarbanion 2 with 3-halo-2-(halomethyl) propenes[1] (1-Cl,I) to 3 provided an early demonstration of the advantages of "mechanistic symmetry" in both C-C bond forming reactions[2] (S_N2 = S_N2' = SET products). In contrast, reaction of 2 with initially symmetric cis-1,4-dihalo-2-butenes leads not to the desired eight-membered ring, compound 5, but rather the product 4 of S_N' closure.



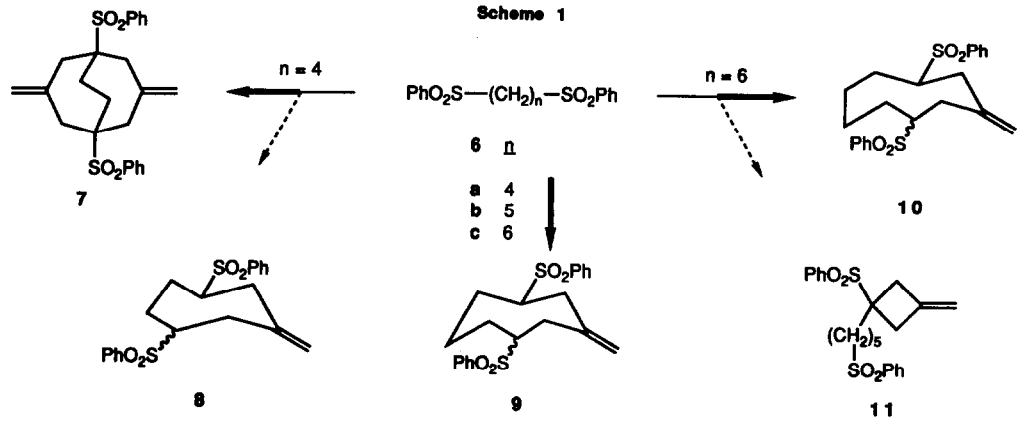
3 2 4 5

It remained to be seen what combinations of carbanion-stabilizing groups (CSGs) would be generally compatible with remote dicarbanion formation in less-constrained substrates, as well as at the mono-alkylated intermediate stages where side reactions might interfere.

We began exploratory studies of 1,n-disubstituted acyclic model compounds with CSGs (corresponding to pKa ≈ 25-35) that could remain as carbon substituents (after reduction) and act as β-leaving groups (e.g. cyano, ester), and with other CSGs that were destined primarily to be eliminated, specifically phenylsulfonyl and phenylsulfinyl groups. Under irreversible carbanion-forming conditions (addition to excess LDA at -78°), the greater kinetic acidity of the latter two groups at α-carbon sites, compared to cyano and ester, allowed Dieckmann or Thorpe reactions to supercede a second proton transfer, as had been noted previously with alkoxide bases.[3] Accordingly, to assess the feasibility of forming 7-, 8- and 9-membered cycloalkadienone

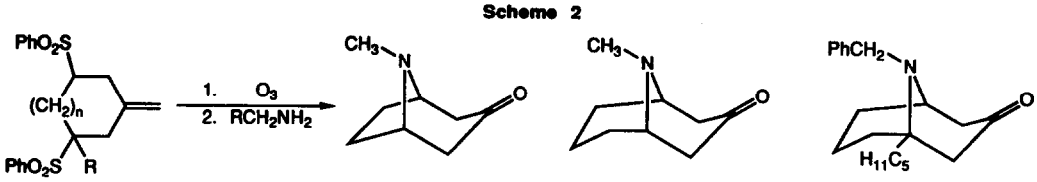
equivalents, we focused initially on α,ω-bis-phenylsulfones[4,5] 6-a,b,c (Scheme 1). Lithiation of the latter (2.2 eqs. n-BuLi in hexane-THF, -78°→0°, 0.5h) was followed by gradual addition of 1-Cl (-78°→25°, 4-6h); workup revealed that these ring sizes were indeed accessible, but with several unexpected results.

Scheme 1



We hypothesize that the propensity of 6-a (but not 6-b or 6-c) to form two rings[5] (7:8 ca. 2:1) arises from extra intramolecular coulombic stabilization[6] of such dilithiated 1,4-dicarbanions. Such dicarbanion triplets[6] should react much slower than the intermediate monocarbanion, which when formed immediately undergoes more rapid intermolecular reaction[7] with a second 1-Cl before proton transfers and two closures (→7). Fortunately, this potentially general complication[6] with 1,3- and 1,4-dicarbanions can be circumvented by substituting α,α'-methallyl diiodide[8] (1-I) for 1-Cl as the bis-electrophile when necessary. Another less general complication, noted only when approaching nine-membered rings (6-c → 10), is intramolecular proton transfer at the monoalkylated stage, which culminates in minor amounts of methylenecyclobutane 11 (identified by cyclobutanone carbonyl absorption at 1800 cm^{-1} in ozonolysis product). With proper attention to the choice of alkylating agent, annulations leading to 8 (86% with 1-I) and 9 (65% with 1-Cl) provide an expeditious and general entry to various tropane and granatane alkaloids, with only two further operations required. After ozonolysis, amine-induced elimination, in situ conjugate addition and subsequent intramolecular closure[9] in aqueous methanol gave high yields (60-65%) of tropinone[10] (13), pseudopelletierine[10] (14) and N-benzyladaline[11] (15), the latter from 1,5-bis(phenylsulfonyl)decane.

Scheme 2

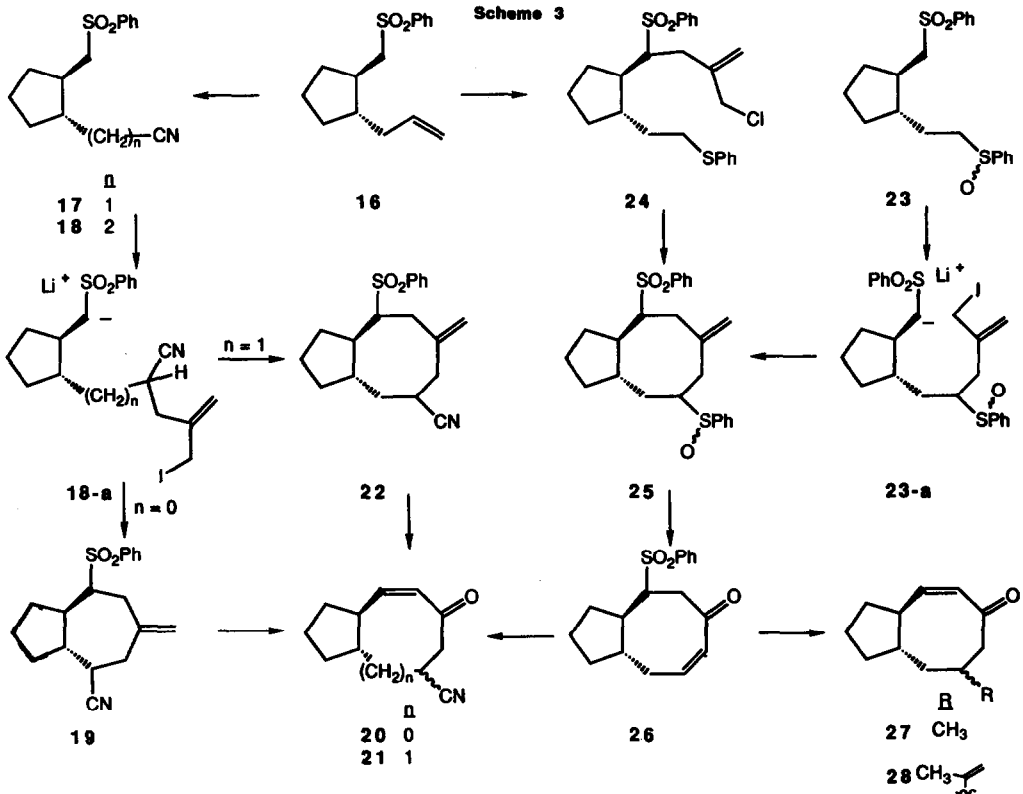


8, 9, 12 (R = n-C_5H_{11}) **13** **14** **15**

We next turned our attention to more rigid 1,4-dicarbanion precursors, such as trans-1,2-disubstituted cyclopentanes, which might resist generating trans-fused bicyclo[3.3.0]octane intermediates at the monoionized stage, thus allowing competitive deprotonation at the second

site. Standard transformations of allylsulfone 16 (beginning with ozonolysis) provided[12] cyano-sulfone 17, mp 116-7°, and the corresponding aldehyde and ester. Of these three, only 17 (and homolog 18) could be dilithiated without self-cyclization; annulation of 17 with 1-I formed the

Scheme 3



5/7 trans-fused product[5] 19 (major isomer, mp 152-3°) in 85-90% yields (1-Cl gave 2:1 adduct, as with 6a). Subsequent ozonolysis and triethylamine-induced elimination in aqueous THF (25°/4h) gave cyano-enone[5] 20. Unfortunately, the 1,5-cyanosulfone homolog 18, mp 97-8°, cyclized to 22 in only ca. 20-25% yield, undoubtedly a consequence of the small size of -C≡N, which does not promote rotation of the staggered allylic side chain (cf. 18-a, Scheme 3) into a gauche arrangement more suitable for cyclization.[13] This prompted replacing the cyano CSG in 18 by the more sterically-demanding phenylsulfinyl in 23, although there arose some apprehension that the alkylated sulfoxide oxygen (cf. 23-a) might intramolecularly displace the neighboring halide, in competition with the more remote sulfone carbanion.[14] In spite of this concern, the direct annulation of dilithiated 23 with 1-I was reproducibly high yielding (80-85% of 25 on 1-5 g scale), proceeding as expected via initial alkylation at the sulfoxide-substituted carbanion site.[14]

Ozonolysis of 25 proceeded uneventfully and the hoped-for regioselective elimination of phenylsulfenic acid was achieved, using triethylamine in aqueous THF (25°, 4h) as acid scavenger. The resulting enone-sulfone 26 (mp 140-1° for major epimer) was shown to undergo conjugate addition with lithium dimethylcuprate (→ 27)[5] and isopropenylmagnesium bromide with CuBr

catalysis (→ 28)[5] without concomitant loss of $PhSO_2H$, which subsequently required >50h at 25° with triethylamine. HCN also added to 26, thus providing structural correlation with cyano-enone 21 formed previously via the lower yielding 18→22 path.

In conclusion, we have formed seven- and eight-membered latent cycloalkenone precursors in high yield and selectively generated individual α,β-unsaturated ketone units without significant deconjugation.[15] The relative ease of β-elimination is $-\phi SOH > -\phi SO_2H >$ -HCN. We are continuing to study the scope and limitations of symmetry-enhanced (n+3) 1,n-dicarbanion cyclizations with various ring sizes and CSG combinations and will report on these developments in due course.[16]

Acknowledgements: Partial support for this research was provided by the National Science Foundation and Merck, Sharp and Dohme. In addition, NSF instrumentation grants assisted in purchasing the VG70-SE mass spectrometer (CHE-850962) and Varian Gemini-300 NMR spectrometer (CHE-8613066) used herein. We also appreciate technical assistance from Dr. Alice M. Bergmann and Dr. Dinesh Sukumaran.

References and Footnotes

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2. For zwitterionic trimethylenemethane equivalents, see B. M. Trost, Angew. Chem. Int. Ed., 25, 1 (1986); for dianionic trimethylenemethane equivalents, see G. A. Molander and D. C. Shubert, J. Am. Chem. Soc., 109, 6877 (1987).
3. S. Oae and X. Uchida, in "The Chemistry of Sulfones and Sulfoxides", S. Patai, Z. Rappoport and C.J.M. Stirling, Eds, John Wiley and Sons, Ltd., New York, 1988, ch. 12.
4. J. K. Crandall and C. Pradat, J. Org. Chem., 50, 1327 (1985).
5. All new compounds, including epimeric mixtures, have been fully characterized by an appropriate combination of IR, ^1H and ^{13}C NMR, and high resolution mass spectroscopy (EI and/or CIMS with isobutane as ionizing gas).
6. A. Streitwieser, Jr., Accts. Chem. Res., 17, 353 (1984) and refs. cited.
7. When 6a di-Li and monolithiated phenyl isopropyl sulfone were generated simultaneously and allowed to compete for 1 eq. of 1-Cl, only the α-alkylated isopropyl sulfone was formed and 6a was quantitatively recovered.
8. K. Schultze, G. Winkler, W. Dietrich and M. Mühlstadt, J. Prakt. Chemie, 319, 463 (1977).
9. cf. T. L. Macdonald and R. Dolan, J. Org. Chem. 26, 4973 (1979).
10. Conformation of this structure was made spectroscopically (ref. 5) and by comparison with an authentic sample.
11. R. K. Hill and L. A. Renbaum, Tetrahedron, 38, 1959 (1982).
12. 16 was prepared by inversion of cis-2-allylcyclopentyl tosylate with α-lithiomethyl phenyl sulfone (60% yield). After ozonolysis, with DMS work-up, cyanosulfone 17 was prepared by aldoxime dehydration; 18, 23 and 24 were prepared after reductive work-up of 16-ozonide and SN2 displacement of 1° alcohol tosylate with CN^- (→ 18) or SPh^- (→ 23 and 24). Full experimental details are provided in the Ph.D. thesis of E. L. Grimm, SUNY at Buffalo, 1990.
13. a) M. E. Jung and J. Gerway, Tetrahedron Lett., 29, 2429 (1988).
    b) S. Cauwberghs, P. J. De Clercq, B. Tinant and J. P. Declercq, Tetrahedron Lett., 29, 2493 (1988).
14. Therefore parallel efforts were made to introduce a methallyl halide side chain unambiguously α- to the sulfone first, by alkylation at the sulfone-sulfide stage (→ 24), before oxidizing the sulfide to sulfoxide. Stepwise annulation of the sulfoxide derived from 24 was not finally achieveable (~45% yield) until three equivalents of LDA was provided. This was required so that the side chain α- to the sulfone could be epimerized, via the carbanion, to a more suitable configuration for internal attack by the lithiated sulfoxide. Details of this approach, which yielded additional novel anionic cyclizations, will be published in the near future.
15. P. Chamberlain and G. H. Whitham, J. Chem. Soc., B, 1131 (1969).
16. Presented in part at the Canadian Society for Chemistry Biannual Symposium on Carbanion Chemistry, Ottawa, Canada, July 23-6, 1989.

(Received in USA 13 April 1990)