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EFFICIENT SYNTHESES OF BREXANE AND HOMOBREXANE MONOFUNCTIONALIZED AT C-2‡

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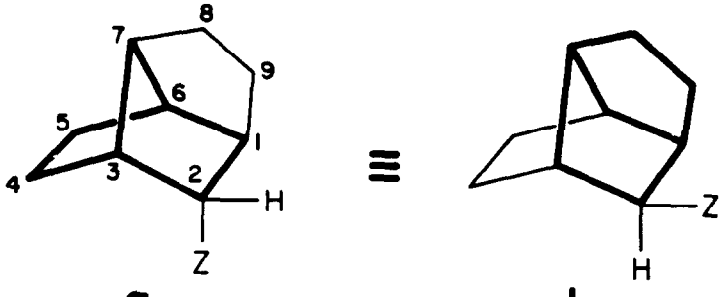
Abstract: An efficient, eight-step synthesis of brexan-2-one has been developed (25.5% overall yield). The strategy also provided two convenient routes to homobrexan-2-one. The schemes can be easily adapted to introduce isotopic labels for mechanistic studies.

Tricyclo[4.3.0.0.^{3,7}]nonane (**1**, Z=H), trivially named "brexane," holds unique interest among fused bridged systems, because it is comprised of two partially superposed norbornyl units (see bold lines in **1a** and **1b**).[1] The parent hydrocarbon and several monofunctional derivatives have served importantly in studies involving carbocations,[2] carbenes,[3] homoenolate ions,[4] and chiroptical behavior.[5] And a trisubstituted brexane played a pivotal role in a total synthesis of the sequiterpene, sativene.[6]

Convenient synthetic routes are presently available to brexanes functionalized in the two-carbon bridges[7] but not to analogs monofunctionalized in the one-carbon bridge (i.e. at C2). Yet, the C2 derivatives are highly desirable for mechanistic investigations because of the unique circumstance that a substituent at that site (**1**, Z = H) is simultaneously exo to one norbornyl unit and endo to the other. Furthermore, only one stereoisomer is possible at C2, because interchange of H and Z produces neither a diastereomer nor an enantiomer but a structure superimposable on the original (i.e. **1a**≡**1b**). Therefore, ionization kinetics and degenerate skeletal rearrangements of compounds such as brexan-2-ol brosylate (**1**, Z=OBs) have the potential to help resolve long-standing debates on how best to interpret the behavior of exo and endo norbornyl substrates.[8]



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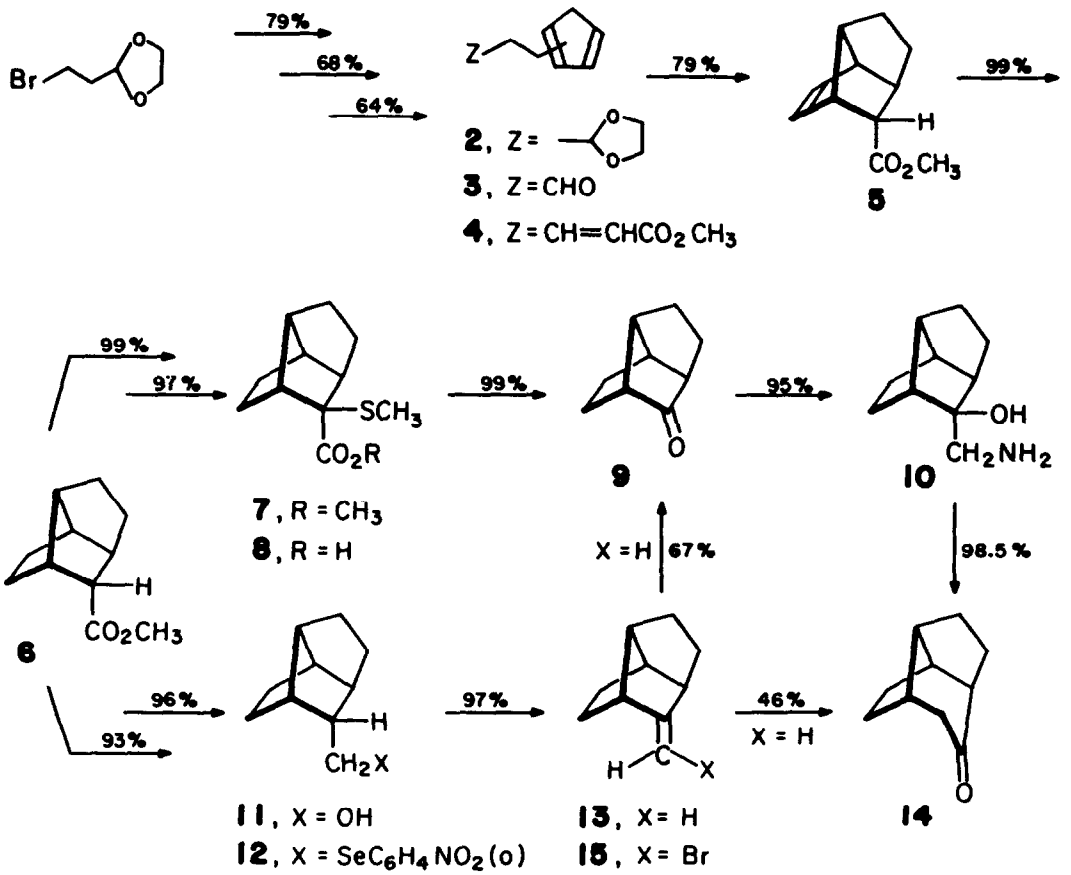
‡Respectfully dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.

Although brexan-2-one has been synthesized before,[5,7c] the published route proceeds through 12 linear steps, is inefficient (overall yield <1%), and involves some laborious and costly procedures. We now describe an efficient, convergent scheme to brexan-2-one. It provides an overall yield of 25.5% and, for the first time, makes this crucial system reasonably accessible for mechanistic exploitation. Furthermore, our route can be easily adapted to provide polyfunctional analogs, isotopically labeled derivatives, and ring-expanded homologs. For example, homobrexane (tricyclo[5.3.0.$0^{4,8}$]decane) is a C_{10} skeleton found in lumibullvalene[9] and believed to be a major conduit in Lewis acid isomerization of [3.3.2] propellanes to adamantane.[10] Homobrexan-2-one (**14**) has been synthesized by Tobe et al. by a multistage route in overall yield of 1%;[10] our current approach produces this ketone in 24% yield.

Our strategy to brexan-2-one (**9**) began with commercially available 2-(2-bromoethyl)-1,3-dioxolane and is summarized in the adjoining scheme. Displacement of bromide by cyclopentadienyl sodium afforded an expected[11] mixture of 2-(2-cyclopentadienylethyl)-1,3-dioxolanes **2** (79% yield), which we hydrolyzed directly to a mixture of 3-cyclopentadienylpropanals **3** (68%).[12] A modified Wittig reaction[13] with methyltriphenylphosphoranylidene acetate converted **3** in 64% yield to a five-component mixture of trienoic esters **4** (two E isomers (92-98%) and three Z isomers (2-8%)). Heating mixture **4** in benzene at 115°C equilibrates the double bonds in the ring and effects



a stereospecific, internal Diels-Alder cycloaddition[14] on the appropriate cyclopentadiene isomer. The product (79% yield) was *endo*-2-methoxycarbonyl-4-brexene (**5**).[15] Catalytic hydrogenation provided 2-methoxycarbonylbrexane (**6**; 99%). The ester appendage was degraded to a ketone by a three-stage sequence[16] that involved: (**i**) treatment of **6** with lithium cyclohexylisopropylamide and dimethyl disulfide to give **7** (99%); (**ii**) saponification to the 2-thiomethyl-2-carboxylic acid **8** (97%); (**iii**) oxidative decarboxylation of the sodium salt with N-chlorosuccinimide to afford brexan-2-one (**9**) in 99% yield. This target ketone (25.5% overall yield from the bromodioxolane) was identical in all respects with an authentic sample.[7c]

To demonstrate the versatility of our scheme, we developed two branch routes to the valuable homolog, homobrexan-2-one (**14**). One branch involved homologation of **9** by successive action of trimethylsilyl cyanide[17] and $LiAlH_4$ to give amino alcohol **10** (95%). Then a Tiffeneau-Demjanov expansion[18] of semipinacol **10** with nitrous acid provided a 98.5% yield of **14**, whose ^{13}C NMR spectrum was superimposable on that of an authentic sample.[19] The overall yield of **14** from the original bromodioxolane was 24%. Our synthesis offers an economical way to label the homobrexane skeleton with ^{13}C for mechanistic studies because the TMSCN reagent can be prepared from ^{13}C-enriched KCN.

In our second branch path to homobrexan-2-one, we reduced ester **6** with $LiAlH_4$ to give alcohol **11** (93%). Then conversion to the seleno ether **12** (96%) with o-nitrophenyl selenocyanate[20] followed by H_2O_2 oxidation afforded 2-methylenebrexane (**13**) in 97% yield.[21] We transformed alkene **13** to ketone **14** directly (46%) by action of cyanogen azide (generated from NaN_3 and CNBr in CH_3CN)[22] and hydrolytic workup. An unexpected substantial by-product (35% yield) in this ring expansion was isolated and shown to be the bromo olefin **15** via ^1H and ^{13}C NMR, mass spectroscopy, etc. Formation of bromo alkenes was not observed earlier by workers who developed this method of ring expansion on numerous systems[22] but evidently arises from bromide in the milieu. This finding could help reveal the types of intermediates involved in the cyanogen azide reaction and might also be explored for possible synthetic potential.

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