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Synthesis of a 6-azaspiro[4.5]decane related to halichlorine and the pinnaic acids

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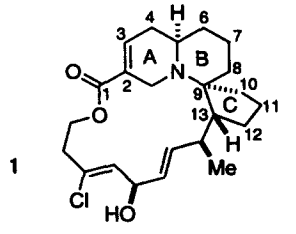
Abstract

Sulfone **15**, derived from D-glutamic acid, and aldehyde **23**, made by diastereoselective alkylation, were linked and elaborated into enamine sulfone **33**. This underwent 5-*exo* radical cyclization to **34**, which was desulfonylated to (−)-**35**, a compound that represents the spirobicyclic core of halichlorine.

Halichlorine (**1**),[1,2] pinnaic acid (**2**),[3] and tauropinnaic acid (**3**)[3] are marine natural products whose biological properties[1,3] may establish them as important lead compounds for the design of drugs to treat diseases associated with inflammation. The absolute configuration of **1** has been established,[2] but that shown for **2** and **3** is an arbitrary assignment made on the basis of the close structural similarity to **1**. The configuration of **2** and **3** at C(17) is unknown.



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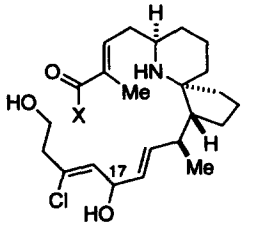

2 X = OH
3 X = $NHCH_2CH_2SO_3H$

Halichlorine inhibits[1] [IC_{50} 7 μg/mL] the expression of vascular cell adhesion molecule-1 (VCAM-1)[4,5] a protein that may be important in the recruitment of mononuclear lymphocytes to inflamed tissue. The pinnaic acids are inhibitors of phospholipase A_2,[3] a property that, likewise, makes them relevant to the medicinal chemistry of inflammation.

Prior synthetic work related to compounds **1–3** includes studies on methods for constructing the 1,4-diene subunit[6] and the spirobicyclic core[7] of **2** and **3**. We report our own route to the spirobicyclic core of halichlorine and the pinnaic acids. Our plan was to link subunits **4** and **5** (Scheme 1) so as to generate

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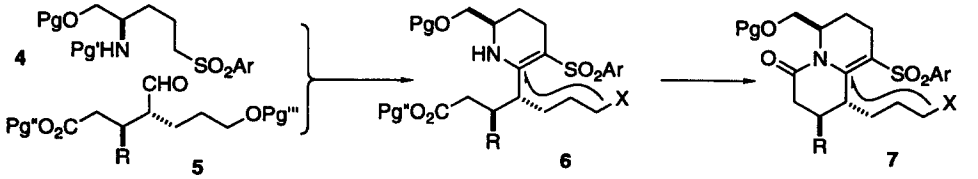
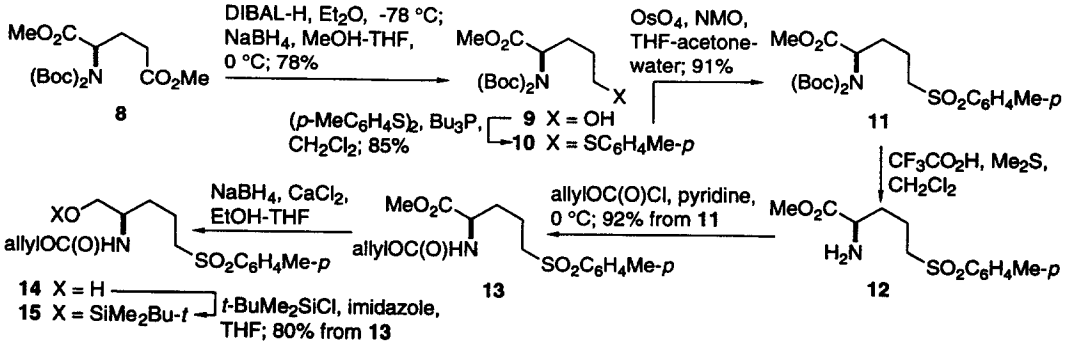
compounds of types **6** and **7**, where X is a homolyzable group. Radical cyclization might then serve to generate the required five-membered ring (see arrows in **6** and **7**). This approach was explored in the following way.



Scheme 1. Pg, Pg', Pg'', Pg'''=protecting groups; Ar=aryl; R=Me or H; X=homolyzable group

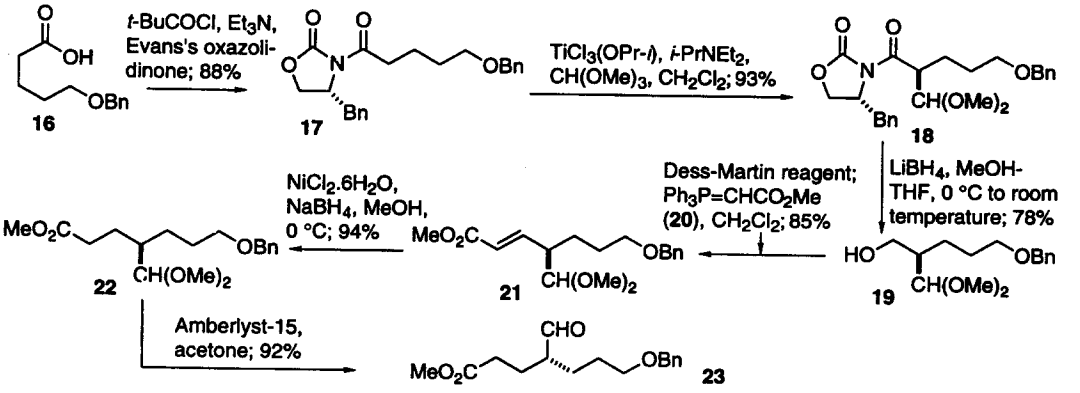
D-Glutamic acid was converted by a very efficient procedure[8] into the diester **8** (Scheme 2). Reduction, first with DIBAL-H (Et_2O, −78°C, 30 min), and then with $NaBH_4$ (MeOH–THF, 0°C, 20 min) gave alcohol **9** (78% overall). The hydroxyl group was replaced by a (*p*-methylphenyl)thio group (**9**→**10**), using (p-$MeC_6H_4S)_2$/Bu_3P[9] (CH_2Cl_2, 3 h; 85%). Oxidation[10] to the corresponding sulfone (**10**→**11**; catalytic OsO_4, *N*-methylmorpholine *N*-oxide, THF–acetone–water, 8 h; 91%) and deprotection of the nitrogen (CF_3CO_2H, Me_2S,[11] CH_2Cl_2, 3 h) took the route as far as amine **12**, and the nitrogen was then reprotected, this time as an allyl carbamate (**12**→**13**; allyl chloroformate, pyridine, 0°C, 30 min; 92% from **11**). Finally, the ester was reduced (**13**→**14**; $NaBH_4/CaCl_2$,[12] EtOH–THF), and the resulting enantiopure[13] alcohol was silylated (*t*-$BuMe_2SiCl$, imidazole, THF, 3 h; 80% over two steps) to afford the desired subunit **15** (cf. **4**).



Scheme 2.

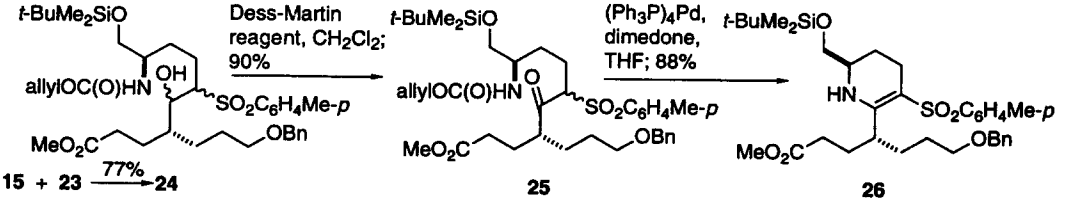
The second component (**23**) (cf. **5**) was made as summarized in Scheme 3. The known acid **16**,[14] readily generated (90%) from δ-valerolactone, was used to acylate[15] *S*-4-(phenylmethyl)-2-oxazolidinone[16] (*t*-BuCOCl, Et_3N, 88%), and the resulting adduct (**17**) was alkylated with $HC(OMe)_3$ [**17**→**18**; $TiCl_3(OPr\text{-}i)$, *i*-$PrNEt_2$, $HC(OMe)_3$, CH_2Cl_2, 0°C, 2 h; 93%].[17] The stereochemistry of **18** was assigned by analogy with related alkylations,[17] and the assignment was confirmed by X-ray analysis of a later intermediate (**28**). The chiral auxiliary was removed[18] ($LiBH_4$, MeOH–THF, 0°C to room temperature, 6 h; 78%), and homologation of the liberated alcohol (**19**) by oxidation (Dess–Martin reagent, CH_2Cl_2, 2 h) to the corresponding aldehyde, and Wittig olefination, using the stabilized ylide **20**[19] (CH_2Cl_2, 8 h), gave the unsaturated ester **21** (85% overall). Saturation of the double bond (**21**→**22**) was effected (94% yield) in MeOH at 0°C, using $NaBH_4$ in the presence of a catalytic amount of $NiCl_2 \cdot 6H_2O$.[20] Finally, acetal **22** was converted into the corresponding aldehyde **23** in dry acetone, by acid-catalyzed exchange, using Amberlyst-15. In order to measure the enantiopurity of **23**, a portion was reduced ($NaBH_4$) and derivatized as its Mosher ester (^{19}F NMR: δ −72.03 ppm). Another portion was

first racemized,[21] and then reduced and derivatized (^{19}F NMR: δ −72.03, −72.01 ppm). Although the chemical shift difference in the latter case was too small to allow baseline separation of the ^{19}F signals, the other spectrum showed a sharp signal with no sign of a shoulder and, on this basis, together with the fact that a later compound in the series (**28**) was a single isomer — as established by its ^{1}H and ^{13}C NMR spectra — we conclude that **23**, and the derived **28**, are enantiopure.



Scheme 3.

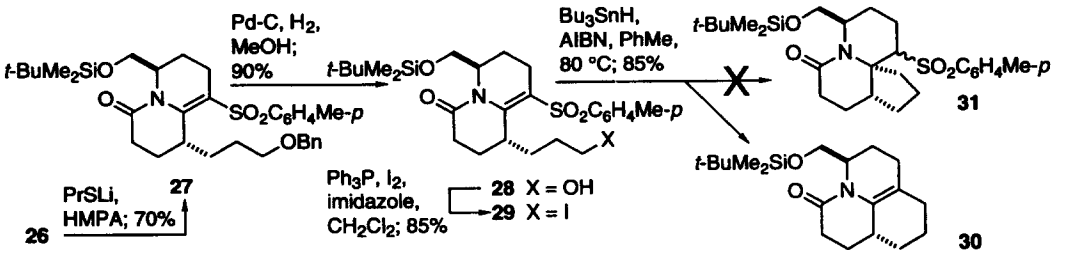
At this point, subunits **15** and **23** were linked (Scheme 4). Deprotonation of **15** (2 equivalents BuLi, THF, −78°C, 45 min), followed by slow addition (over 20 min) of a THF solution of aldehyde **23**, gave a mixture of diastereoisomeric hydroxy sulfones (**24**, 77%). These were easily oxidized to the corresponding keto sulfones **25** by the Dess–Martin reagent (90%) and, when the allyloxycarbonyl group was removed [$(Ph_3P)_4Pd$, dimedone, THF, 2 h], the desired sulfonyl enamine **26** was isolated in 88% yield.



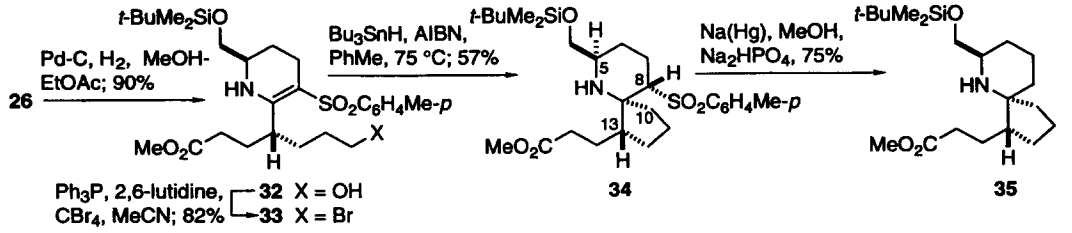
Scheme 4.

Our original plan had been to convert **26** into a compound of type **7** (see Scheme 1) and, to this end, **26** was treated with PrSLi in HMPA at room temperature (Scheme 5). Under these conditions,[22] the required lactam **27** could be isolated (70%), together with a small amount (ca. 10%) of the simple ester hydrolysis product (CO_2H instead of CO_2Me in **26**). Debenzylation of **27** (H_2, Pd–C, MeOH; 90%) gave alcohol **28** (Scheme 5), whose structure was confirmed by X-ray analysis. Replacement of the hydroxyl by iodine (**28**→**29**; Ph_3P, I_2, imidazole, CH_2Cl_2; 85%) served to generate the precursor for the intended radical cyclization (**29**→**31**). The bicyclic structure of **29** had been specifically set up so that spirocyclization could occur only in the desired stereochemical sense but, in the event, treatment of **29** in PhMe at 80°C with toluene solutions of Bu_3SnH (0.1 M) and AIBN (0.03 M), both added over 5 h, gave instead the product of 6-*endo* closure (**30**). Fortunately, the desired *exo* closure could be effected by carrying out the radical cyclization at an earlier stage. To accomplish this, ester **26** was subjected to hydrogenolysis (Scheme 6, **26**→**32**; H_2, Pd–C, MeOH–EtOAc; 90%), and the liberated hydroxyl was replaced by bromine (**32**→**33**; Ph_3P, CBr_4, 2,6-lutidine, MeCN, 0°C, 30 min; 82%). When bromide **33** was subjected to our standard conditions for radical cyclization (see above), it was converted into the

desired spirocycle **34**, which was isolated in 57% yield, together with the product of simple reduction (replacement of Br by H; ca. 30%).



Scheme 5.



Scheme 6.

The results of the radical reactions with **29** and **33** suggest the operation of subtle conformational and/or steric effects that determine whether an *exo* or *endo* pathway is followed. Possibly, electronic factors are also involved. Compound **34** was obtained as a single isomer. The material is an oil, and its configuration was established by TROESY NMR experiments, the essential observations being significant NOE enhancements between H_5 and H_{10}, and between H_8 and H_{13}. Finally, desulfonylation[23] [10% Na(Hg), MeOH, Na_2HPO_4, 10 h; 75%) gave the 6-azaspiro[4.5]decane **35**, $[\alpha]_D$ –6.29 (*c* 0.27, CH_2Cl_2), representing the core of halichlorine.

All new compounds were characterized by combustion analysis and/or spectroscopic measurements, including accurate mass measurement.

Acknowledgements

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