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STEREOSPECIFIC TOTAL SYNTHESIS OF (±)PENTENOMYCINS BY FLASH VACUUM THERMOLYSIS OF SUBSTITUTED TRICYCLO[5.2.1.$0^{2,6}$]DECENONES

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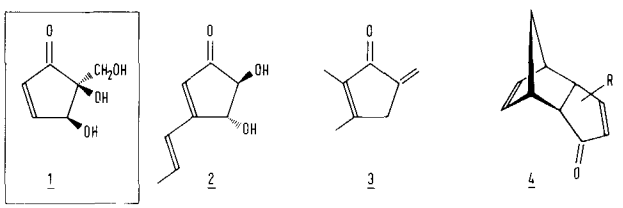
Abstract. *The synthesis of 4-functionalized tricyclo[5.2.1.$0^{2,6}$]decenones 9, starting from furans, is described. These structures are shown to be suitable precursors for the synthesis of cyclopentenoids such as pentenomycin and analogs.*

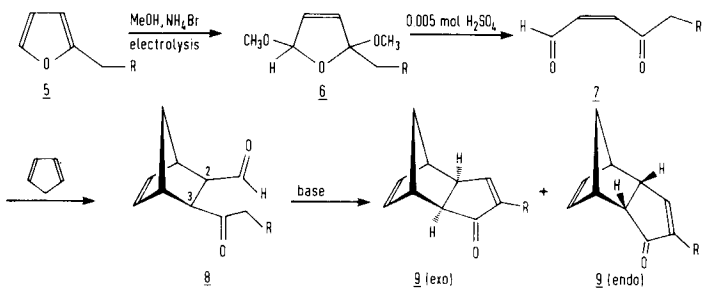
Natural products containing the highly oxygenated cyclopentanoid skeleton have recently attracted considerable attention because in many cases they exhibit interesting biological activities. This rapidly growing class of antibiotics includes amongst others pentenomycin 1, terrein 2 and methylenomycin B 3[1].
Although the basic structures of these compounds seem relatively simple, their sensitivity towards acids and bases requires a well-designed synthetic strategy.



Our approach to this class of natural products is based on the consideration that these cyclopentenones are retrosynthetically connected with cyclopentadienones. Since these cyclic dienones are known to have a strong tendency to dimerize which prevents their use as synthetic building blocks[2], we sought their synthetic equivalents.
The tricyclo[5.2.1.$0^{2,6}$]decenone system 4 is particularly suitable to serve this purpose as it essentially constitutes a cyclopentadienone in which one of the two double bonds is being masked in the crossed Diels-Alder adduct with cyclopentadiene. Chemical transformation of the remaining enone system in 4 followed by thermal cycloreversion regenerates the double bond and produces a functionalized cyclopentenone. The net result of this sequence is actually selective transformation of one of the olefinic bonds in cyclopentadienone.
Recently, we used this strategy for the synthesis of terrein 2[3]. In this paper we wish to report on the synthesis of pentenomycin 1, an antibiotic isolated from *Streptomyces eurythermus*[4].
We figured that 4-hydroxymethyltricyclodecenone 9 (R=CH_2OH) would be an ideal precursor for pentenomycin.

To this end, a general and efficient synthesis of 4-functionalized tricyclodecenones 9 was developed starting from readily available furan compounds (scheme I).

Scheme I



R = H, CH_3, C_5H_{11}, SCH_3, $CO_2C_2H_5$, CH_2OH, CH_2OCH_3, CH_2OAc

Electrolysis of furans 5 at -20 °C in MeOH in the presence of NH_4Br led quantitatively to dihydrodimethoxyfurans 6, which on careful hydrolysis gave *cis*-enediones 7 (cf. ref. 5). These enediones reacted smoothly in a Diels Alder reaction with cyclopentadiene to afford *endo-cis*-norbornene adducts 8 in quantitative yields. Subsequent intramolecular aldol condensation with base (t-BuOK or NaOH in MeOH) gave a mixture of *exo*- and *endo*-tricyclodecenones 9 in overall yields ranging from 50-90% based on 5. The ratio of *exo* and *endo* products appeared to be strongly dependent on the nature of the substituent R. Carbanion stabilizing groups such as SCH_3 or CO_2R led exclusively to the *endo* products whereas for R=CH_3 and CH_2OCH_3 an *endo/exo* ratio of about 1:1.5 was observed. Clearly, under the applied basic conditions intramolecular aldol closure competes with epimerization at C_2 or C_3 in 8, which initially affords a *trans*-2,3-disubstituted norbornene. In such a structure intramolecular ringclosure will favor the thermodynamically more stable *exo*-tricyclodecenone 9.

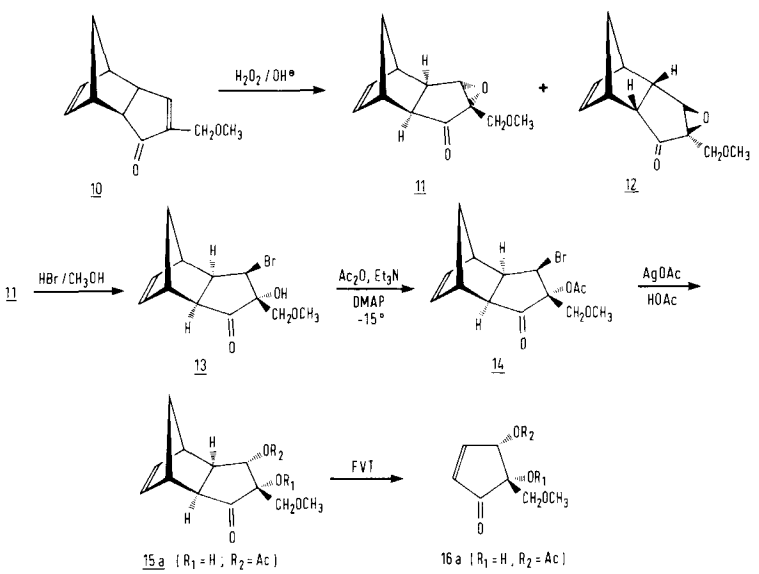
With an expedient route to methyl protected 4-hydroxymethyltricyclodecenone 10 available, we next directed our attention to the vicinal *cis*-hydroxylation of the enone double bond in this compound (scheme II).

Selective epoxidation of the *endo/exo* mixture of 10 with H_2O_2/OH^- afforded epoxides 11 and 12 in 80% yield. These epoxides appeared to be very reluctant to undergo hydrolysis. This is due to steric interaction which in both epoxides seriously hampers Sn_2-type substitution reactions. After extensive experimentation we found that *exo*-epoxide 11 can be converted into the bromohydrin 13 by treatment with a concentrated solution of HBr in CH_3OH (60-80% isolated yield). Under these conditions the *endo*-isomer 12 was recovered unchanged. When more drastic conditions were applied, only complete deterioration of both epoxides was observed.

Alcohol 13 was transformed into the acetate 14 by treatment with acetic anhydride and DMAP/Et_3N at -15 °C. These mild conditions are essential to avoid the reformation of epoxide 11 which readily takes place.

As expected the displacement of bromine by an hydroxyl or acetate function turned out to be extremely troublesome due to steric hindrance. Both NaOAc and KOAc in various solvents and under a variety of conditions did not lead to substitution. Eventually, we found that AgOAc in glacial

Scheme II



acetic acid at reflux temperature gave in a stereospecific reaction the acetate alcohol 15a in 80% yield. Both the inversion of configuration at the carbon of substitution, and the migration of the acetate function, can be explained by participation of the 4-acetate function which produces a cyclic oxonium ion[6] and AgBr. Hydrolysis of this ion with water present in AcOH, then led to the thermodynamically more favored acetate 15a.

Unambiguous prove for the *cis*-configuration of the acetate and hydroxyl function in 15a was provided by the X-ray analysis of its diacetate 15b (R^1=Ac; R^2=Ac)[7].

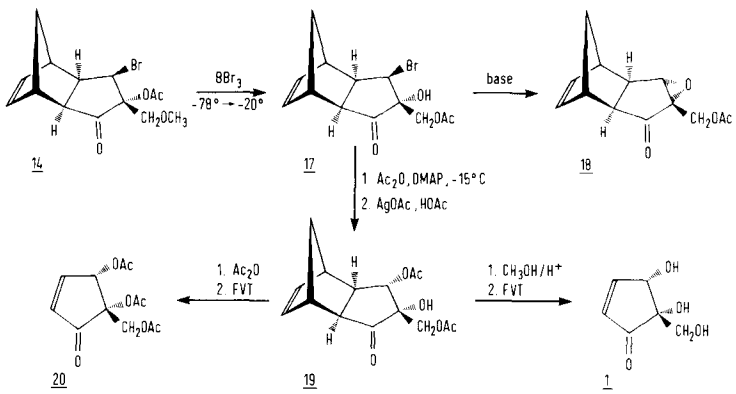
Monoacetate 15a was converted into diol 15c (R^1=H; R^2=H) by acid catalyzed transesterification in CH_3OH.

After having successfully completed the crucial *cis*-hydroxylation reaction, the compounds 15 were subjected to the thermal demasking step. Flash vacuum thermolysis of diol 15c at 525 °C / 0.1 Torr proceeded smoothly to afford methyl pentenomycin 16c in quantitative yield. In a similar way mono- and diacetate 15a and 15b gave cyclopentenones 16a and 16b, respectively.

To complete the synthesis of pentenomycin, all that remained was deprotection of the primary alcohol function. We found that this demethylation can be best carried out in the stage of bromoacetate 14 with BBr_3. Adding 1,2-equivalent BBr_3 at -78 °C to 14 and then warming up to -20 °C, gave an excellent yield of alcohol acetate 17 (scheme III).

The unanticipated migration of the acetate function can be rationalized by an acid catalyzed intramolecular transesterification reaction which produces the thermodynamically most stable acetate which apparently is 17. Its structure was proven by its rapid conversion into the epoxide 18 by treatment with a little base[8]. Acylation of 17 with Ac_2O and DMAP produced the corresponding diacetate which upon treatment with AgOAc in HOAc gave alcohol 19 in an excellent yield (66% from 17). Acid catalyzed methanolysis of 19 led quantitatively to the corresponding triol which upon flash vacuum thermolysis (525 °C / 0.04 Torr) was smoothly transformed into (±)pentenomycin 1 in 50% yield.

Scheme III



The spectral data of 1 / IR ν (neat) 3400, 1710, 1590 cm^{-1}; UV (CH_3OH) λ_{max} 212 nm, ε 3000); ^1H NMR (D_6 acetone) δ 7.7 (d of d, J_{H_2,H_3}=6 Hz, J_{H_3,H_4}=2.4 Hz, H_3), 6.3 (d of d, J_{H_2,H_3}=6.0 Hz, J_{H_2,H_4} < 2 Hz, H_2), 4.85 (broad s, H_4), 3.7 (AB q, J_{AB}=9 Hz, $-CH_2O-$) ppm / are entirely consistent with the pentenomycin structure[4].

We also prepared the triacetate of pentenomycin 20 by acylation of 19 followed by FVT (500 °C / 0.04 Torr, yield: 100%). Its spectral data were also in full accord with those published[4].

The work presented here demonstrates the versatility of our synthetic strategy to pentenomycin and a variety of its derivatives. It may be expected that these structures will have interesting biological properties[9].

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