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Approaches Towards Indolic Analogues of Cephalotaxine *via* a *spiro*-Cyclohexene Strategy

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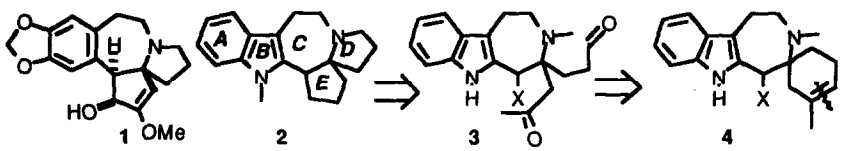
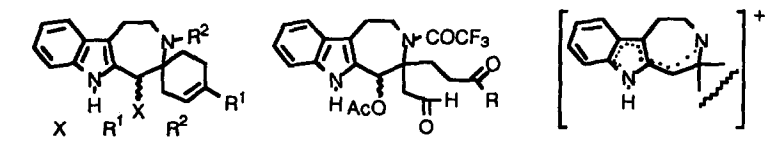
Abstract: *Highly functionalized (dialkyloxo)indoloazepines* ***10, 11, 34*** *and the pyrroloazepinoindole* ***35*** *were prepared via oxidative cleavage of the corresponding spiro-cyclohexene derivative. Tetracycle* ***35*** *bears carbons and functionalities required for building the new ring system* ***2****.*

The cytotoxic activity[1] of natural cephalotaxine (**1**) esters such as harringtonine[2] has motivated our interest in the synthesis of indolic analogues with the hitherto unknown ring system **2**.



Generation of the two five membered rings D and E was devised through a double ring closure of a suitably 2,2-disubstituted-1,2,4,5-hexahydro-3*H*-azepino[4,5-b]indole **3** (X=OH or equivalent). Access to **3** was considered possible *via* an oxidative cleavage of the *spiro* cyclohexene ring in **4**, whose synthesis was scheduled along our recently reported "homo-Pictet-Spengler" approach.[3]



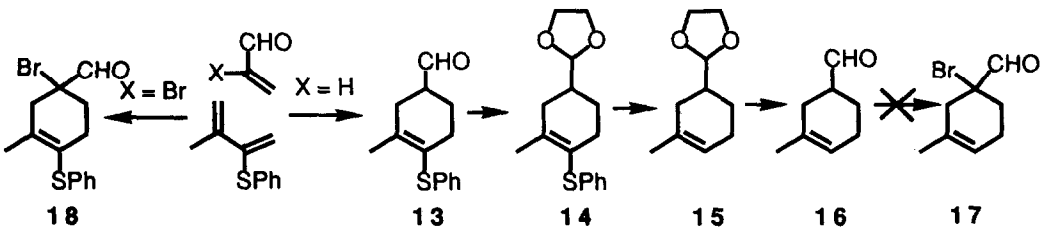
	X	R^1	R^2
5	OAc	H	H
6	OMe	H	H
7	OAc	H	$COCF_3$
8	OAc	Me	H
9	OAc	Me	$COCF_3$

10 R = H
11 R = Me

12

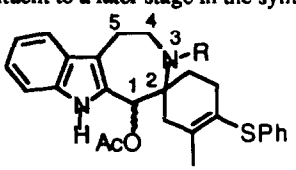
Scheme 1

Chemoselectivity of the oxidation step in the presence of the fragile indole nucleus had first to be tested. The easily accessible[3] model compounds **5** and **8**[4] were thus ozonolyzed (O_3,CH_2Cl_2, -40°C, then Me_2S) in the form of their trifluoroacetamides **7** and **9**[5] (scheme 1), and indeed yielded the unstable tricyclic derivatives **10** (55%, rec) and **11** (82.5%, rec). When heated in methanol, **5** underwent quantitative replacement of OAc by OMe yielding **6**, which demonstrated susceptibility to nucleophilic attack onto the delocalized cation **12** that further justified the above design.

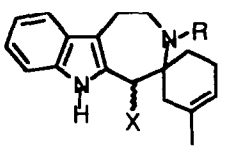


Scheme 2

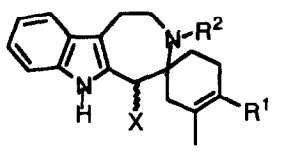
Turning to the synthesis of **4**, 2-methyl-4-formylcyclohexene **16** was first prepared in four steps from **13**, resulting itself from a Diels-Alder cyclization between acrolein and 3-methyl-2-phenylthiobutadiene[6] (scheme 2). The protected aldehyde **14** was oxidized to a sulfone ($KHSO_5$)[7], then hydrogenolyzed (Na,Hg)[8] to **15**, and deprotected. However, attempts at bromination of **16** to give **17** using $CuBr_2$ [9] failed, in contrast with previous results[3]. Alternatively we found that Diels-Alder cyclization of 3-methyl-2-phenylthiobutadiene with 1-bromoacrolein smoothly yielded **18** (70%), which prompted us to postpone the removal of the SPh substituent to a later stage in the synthesis.



19 R = H
20 R = Ac
21 R = $COCF_3$



	X	R
22	OH	Ac
23	OAc	Ac
24	OAc	$COCF_3$
25	OAc	H
26	OH	H



	X	R^1	R^2
27	OH	SPh	Ac
28	H	H	Ac
29	H	H	$COCF_3$

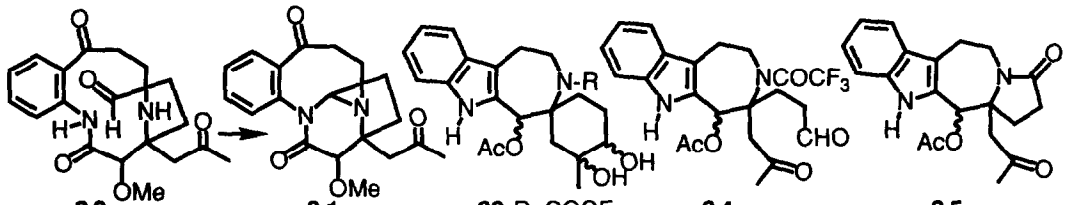
Scheme 3

Run Number	Starting material	Reaction Conditions	Isolated Compounds (Yields)
(1)	**20**	Raney Ni-I, EtOH, -20°C, 4h	**27**(75%)
(2)	**20**	Raney Ni-I, EtOH, 20°C, 2h	**22**(19%);**28**(44%)
(3)	**20**	Raney Ni-II, EtOH, 20°C, 24h	**23**(37%);**28**(29%);**29**(11%)
(4)	**21**	Raney Ni-III, EtOH, 20°C, 1h	**24**(35%);**29**(35%)
(5)	**21**	Raney Ni-III, EtOH/acetone,refl.,1h	**24**(71%)
(6)	**19**	Raney Ni-III, EtOH/acetone,20°C,0.5h	**25**(15%)

Table 1

Bromoaldehyde **18** was then reacted with tryptamine (AcOH, 70°C) to give the expected *spiro* compound(s) **19** (scheme 3), whose acetamide **20** and trifluoroacetamide **21**[10] were prepared. Getting rid of the thiophenyl substituent here again proved to be difficult: $KHSO_5$ oxidation of **20** stopped at the sulfoxide

level, precluding desulfuration of the sulfone. Raney nickel hydrogenolyses of **19-21** were then thoroughly studied using various catalysts[11] and reaction conditions. Apart from desired cleavage of the phenylthio appendage, hydrogenolysis or hydrolysis of the 1-acetyl substituent occasionally resulted in generation of the secondary alcohol, or in reduction. Table 1 reports some of these results, giving rise to the suitable (**22-25**) or unsuitable (**27-29**) derivatives. While the targetted intermediate **25** was produced in low yield from **19** (run 6), **24** was satisfactorily obtained from **21** (run 5) and induced us to further deprotect its basic nitrogen. Treatment of **24** with K_2CO_3 in MeOH indeed hydrolyzed both acyl groups to the aminoalcohol **26** (70%).



Scheme 4

Oxidative cleavage of the cyclohexene ring in the most accessible compounds **24** and **26** was further explored. Ozonolysis of **26** hydrochloride in MeOH, followed by reduction with thiourea, yielded a complex mixture from which the overoxidized rearranged derivative **31**[12] was isolated (8%) with difficulty (scheme 4). Oxidation of both ethylenic and indole double bonds in **26** presumably generated the bicyclic intermediate **30** which cyclized to **31**[13]. In contrast to the ozonolysis of **7** and **9**, but by analogy with that of **26**, ozonolysis of trifluoroacetamide **24** indicated some hindrance to the access of ozone to the ethylenic double bond with respect to the faster cleavage of the indole, as shown by the absence of indolic material (uv) in the complex reaction mixture. The difficulty was partly circumvented by performing a milder two-step oxidation of the ethylenic double bond: osmylation of **24**[14] (OsO_4,py,0°C,15h, then $NaHSO_3$) gave diol **32** whose sodium periodate oxidation generated the unstable ketoaldehyde **34** with a low 10% yield. Attempts to hydrolyze the trifluoroacetamide group in **32** or **34** were unsuccessful, so that we turned to the osmylation of the secondary amine **25**. Diol **33** resulted (19%, rec), and was further cleaved (and cyclized) by $NaIO_4$ to the octahydropyrroloazepinoindole **35** (99% from **33**).

These last results point out the unexpected modification of reactivity of the ethylenic double bond (or of the derived diol) towards oxidation when passing for example from **7** to the isomeric **24**. This impediment prevented us from completing the final ring closure. However experience gained during exploration of this route has proved of great value for related synthetic approaches which are under current study in these laboratories.

References and Notes:

1. Zhou, J.Y.; Chen, D.L.; Shen, Z.; Koeffer, H.P. *Cancer Res.*, **1990**, *50*, 2031-2035. Graifer, D.M.; Tuebaeva, R.M.; Matasova, N.B., Fedorova, O.S.; Karpova, G.G.; Aitbrehozkina, N.A. *Mol. Biol*, **1990**, *24*, 1679-1685. Liu, Y.G. *Can.* CA 1, 267, 845 17 April 1990 (*Chem. Abst.*, **1990**, *113*, 197998).
2. Abraham, D.J.; Rosenstein, R.D.; McGandy, E.L. *Tetrahedron Lett.*, **1969**, 4085-4086.
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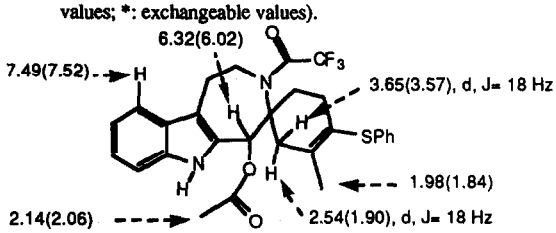
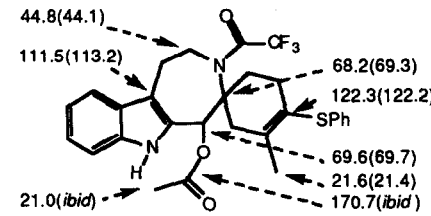
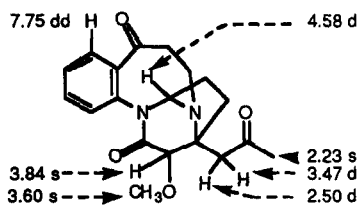
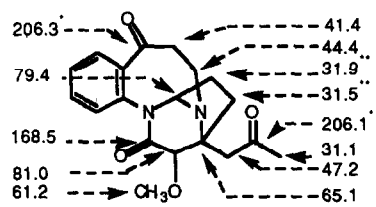
4. Unless specified, all compounds are mixtures of two diastereomers (in the racemic form).
5. All new compounds were fully characterized by their spectroscopic data (uv, ir, ^{1}H and ^{13}C nmr) and exhibited the correct molecular peak on their mass spectra (see also [10] and [12]).
6. The phenylthio substituent is known to revert the regioselectivity of the cyclization (Proteau, P.J.; Hopkins, P.B. *J.Org. Chem.*, **1985**, *50*, 141-143).
7. Trost, B.M.; Curran, D.P. *Tetrahedron Lett.*, **1981**, *22*, 1287-1290.
8. Trost, B.M.; Arndt, H.C.; Strege, P.E., Verhoeven, T.R. *Tetrahedron Lett.*, **1976**, 3477-3478.
9. King, C.L.; Ostrum, G.K. *J. Org. Chem.*, **1964**, *29*, 3459-3461.
10. The two diastereomeric racemates **21a,b** could be chromatographically separated at this stage; **21a**, more polar, and **21b**, less polar, exhibited nearly identical spectral properties. Chemical shifts (^{1}H and ^{13}C) are given in ppm (brackets: **b** values; *: exchangeable values).



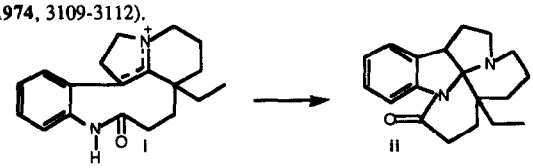


11. Raney Nickel-I : Billica, H.R.; Adkins, H. in *Organic Syntheses, Coll. Vol. III* p. 176. Wiley Ed., New-York 1964. Raney Nickel-II : by washing Nickel I with distilled water (5 x 100 ml/0.1 mol), 95 % ethanol (3 x 100 ml) and absolute ethanol (3 x 100 ml). Raney Nickel-III : Van Driel, H.; Van Reijendam, J.W.; Buter, J.; Wynberg, H. *Synthetic Commun*, **1971**, *1*, 25-27.
12.





13. The last step in the reaction is reminiscent of the obtention of **ii** from intermediate **i** (Hugel, G.; Lévy, J.; and Le-Men, J.; *Tetrahedron Lett.*, **1974**, 3109-3112).



14. The reaction was performed on the isolated less polar isomer **24b**.

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