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Synthesis of Conformationally Restricted Analogues of the Tryptophanyl tRNA Synthetase Inhibitor Indolmycin

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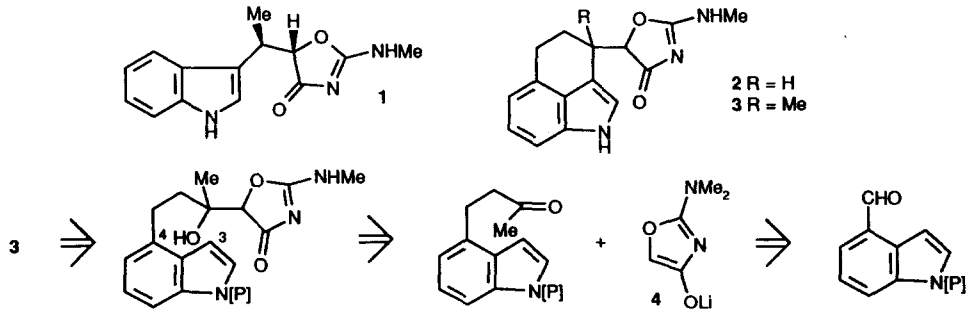
Abstract: The synthesis of conformationally constrained indolmycin analogues is described. Compounds in which the oxazolinone group is separately linked to the indole C-4 position rather than C-3 are also prepared. A highly diastereoselective Michael addition of an oxazolinone lithium enolate to an αβ-unsaturated 2-oxindole and the facile regioselective addition of phenylselenyl chloride to a β-disubstituted enolate are reported. Copyright © 1996 Elsevier Science Ltd

Selective inhibition of specific bacterial amino-acyl tRNA synthetases has attracted much theoretical and practical interest as the mechanism of action for novel therapeutic antibacterial agents.[1] The natural product indolmycin **1**, a potent and selective inhibitor of the bacterial tryptophanyl enzyme, has been studied widely since it was first reported by Rao in 1960.[2] Several syntheses of indolmycin exist[3] and various structural modifications have been reported; principally substitutions on the oxazolinone ring.[4] Our recent investigation of the role of the methyl substituent on the carbon atom that separates the two rings of indolmycin, indicated that the enzyme inhibitory activity of substituted analogues is related to predictable conformational preferences.[5] The synthesis of a conformationally restricted version such as **2** or **3** therefore became an important objective.

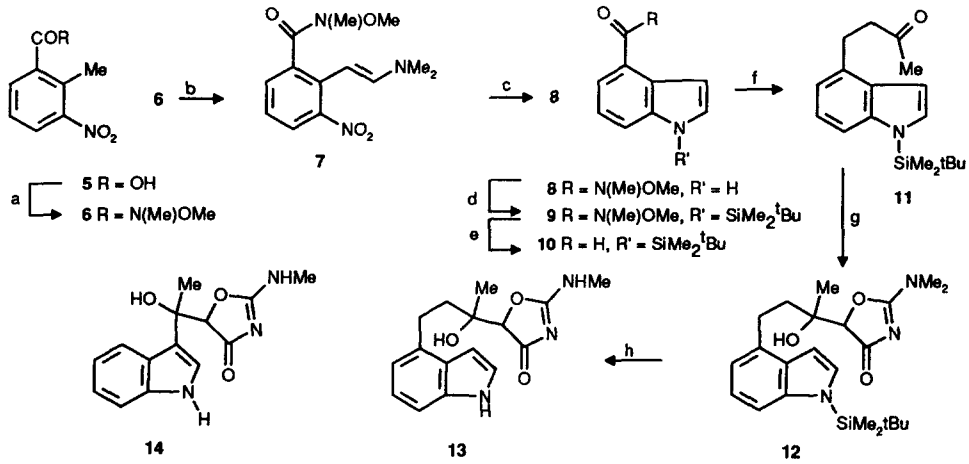


Scheme 1

Such substituted fused tricycles represent a novel compound class and our first strategy envisaged a disconnection sequence (**Scheme 1**) in which an aliphatic chain, extending from the indole C-4 position, is closed to form the third fused ring making use of the inherent nucleophilicity of the indole C-3 position. We

had previously demonstrated that the oxazolinone lithium enolate **4** will react with an analogous ketone to give a stable adduct.[5]

The 4-functionalised indole starting material was constructed by a modified Leimgruber-Batcho synthesis (**Scheme 2**) using a Weinreb amide as a masked aldehyde.[6] 2-Methyl-3-nitrobenzoic acid **5** was converted to the hydroxamide **6**, and reacted with dimethylformamide dimethyl acetal to give the dimethylaminomethylene adduct **7** in 97% overall yield. Reduction of the nitro group of **7** was complicated by cyclisation of the less soluble hydroxylamine intermediate to give a stable N-hydroxyindole.[7] Medium pressure hydrogenation over a prehydrogenated palladium catalyst in a 1:5 mixture of toluene and THF was necessary to achieve 81% indole formation. N-Silylation of the resulting Weinreb amide **8** to give **9** permitted an efficient reduction to the aldehyde **10** using DIBAL in 89% overall yield. Extension of the carbon chain was achieved by a Wittig condensation with acetylmethylenetriphenylphosphorane and reduction of the resulting conjugated ketone performed by hydrogenation over a partly deactivated palladium catalyst to afford **11** in 58% overall yield.[8] Reaction of this ketone with the enolate **4** afforded two diastereomers of **12** in quantitative yield.

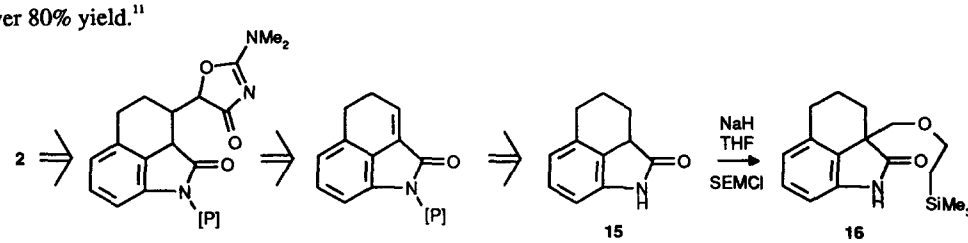


a) $(COCl)_2$, CH_2Cl_2, DMF then NH(Me)OMe, pyridine; b) $(MeO)_2CHNMe_2$, DMF reflux; c) H_2/Pd on C, THF, Toluene; d) NaH, THF, TBDMSCl; e) DIBAL, CH_2Cl_2; f) Ph_3P=CHCOMe, 1,4-dioxane, reflux then H_2/Pd on C, EtOAc; g) **4**, THF; h) NH_2Me, sealed tube then CsF, silica gel, aq MeOH.

Scheme 2

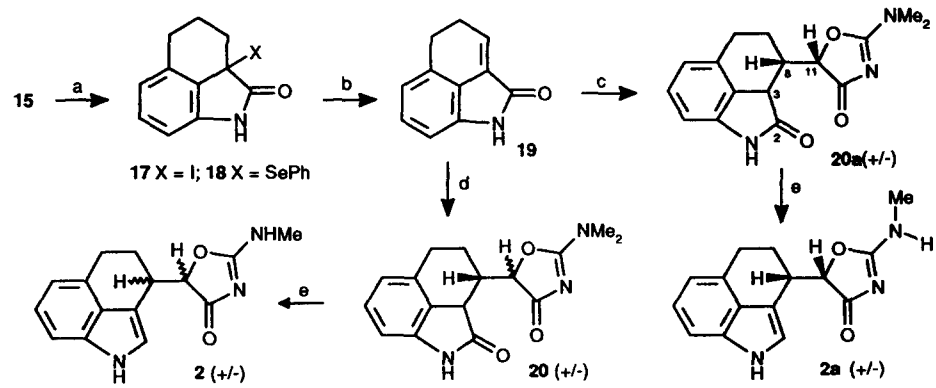
This sequence was successful in generating the required carbon framework; however, no conditions were discovered which would permit the ring closure to form the fused [5,6,6]tricycle. The tertiary hydroxyl group of **12** could neither be functionalised further nor made to eliminate. For example, the 3-position of the indole reacted preferentially with trifluoroacetylisocyanate and attempts to make the O-triflate lead to rearrangement products and the competing reverse aldol reaction. However, this synthesis does provide access to the corresponding open chain form **13**; an homologous geometrical isomer of the hydroxyindolmycin **14**, recently reported by us as an efficient inhibitor of bacterial tryptophanyl tRNA synthetase.[5] Transamination of the oxazolinone dimethylamino group of **12**, followed by removal of the silyl protecting group using caesium fluoride, afforded the two diastereomers of **13** in 85% overall yield. Studies by n.m.r. indicate that, in common with indolmycin, both diastereomers exist in solution as 2:1 mixtures of exocyclic rotational isomers.[9]

Our alternative strategy was to couple the oxazolinone to the completed fused [5,6,6]heterocycle. The intended approach utilised the readily available oxindole **15**, which after appropriate protection, would be converted to an αβ-unsaturated amide capable of adding the oxazolinone enolate **4** by a Michael reaction. The preparation of **2** would be completed by subsequent reduction and transamination (**Scheme 3**). A SEM group was initially chosen to protect the oxindole nitrogen of **15** while the double bond was introduced; however, alkylation occurred overwhelmingly at *carbon*, with concomitant formation of a quaternary centre,[10] to give **16** in over 80% yield.[11]



Scheme 3

The need for N-protection was obviated as we can report that this regiospecificity was also demonstrated by heteroatomic electrophiles: both the unstable 3-iodo **17** and the 3-phenylselenyl **18** adducts were prepared from **15** (**Scheme 4**) in yields of between 65% and 85%. Mild oxidation of **18** gave a selenoxide which readily eliminated to form the stable unsaturated amide **19** in 50% overall yield. Low temperature addition of enolate **4** afforded the tetracycle **20a** in almost quantitative yield. In theory, four pairs of diastereomers are possible but at low temperature, just *one* racemic diastereomer formed selectively. On warming epimerisation at C-11 occurred, a process which could be driven to completion by addition of tetramethylguanidine, resulting in an equimolar mixture of two diastereomeric racemates (**20**).

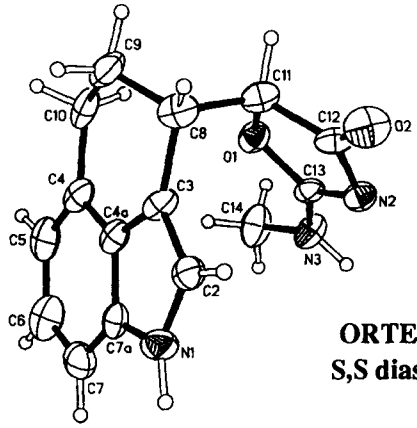


a) NaH, THF then I_2 or PhSeCl; b) $NaIO_4$, aq EtOH, Δ; c) **4**, THF -78°C to -20°C;
d) **4**, THF -78°C to RT then TMG; e) DIBAL, THF, CH_2Cl_2, -78°C then $MeNH_2$, 0°C, sealed tube

Scheme 4

Isomer **20a** was specifically reduced at the oxindole C-2 position using diisobutylaluminium hydride. No measurable epimerisation of the C-8 or C-11 stereocentres occurred and subsequent transamination afforded **2a**

as a crystalline solid (60% over two steps); the structure of this compound was proven by X-ray crystallography to have the C-8 (S), C-11 (S) relative stereochemistry.[12] The corresponding mixed diastereomers (2) were formed when the isomeric mixture **20** was subjected to the same conditions.



ORTEP Projection of 2a
S,S diastereomer depicted

Both racemic diastereomers of **2** were inhibitors of tryptophanyl tRNA synthetase from *Staphylococcus aureus*. Their I_{50} values were between 5 and 10 times greater than that for indolmycin and both isomers showed weak antibacterial activity. By contrast, neither isomer of **13** proved to be a measurable inhibitor of the enzyme nor possessed any antibacterial activity.[13]

REFERENCES AND NOTES

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8. Over reduction of the intermediate αβ–unsaturated ketone to the saturated alcohol occurs during hydrogenation with the most active palladium catalysts.
9. ^{1}H NMR data for **13**: δ $(CD_3)_2C$=O, More Polar Isomer: 1.4 (3H, s, MeCq), 2.00-2.13 (2H, m, CH_2Cq), 2.95-3.08 (5H, m, $ArCH_2$, NMe), 4.00, 4.12 (1H, 2s, OH), 4.60, 4.68, (1H, 2s, CHC=O), 6.55-7.3 (5H, m, Ar-H), 7.5, 7.7 (1H, 2bs, N=CNH), 10.2 (1H, bs, NH indole); Less Polar Isomer: 1.31, 1.37 (3H, 2s, MeCq), 1.98 -2.13 (2H, m, CH_2Cq), 2.95-3.10 (5H, m, $ArCH_2$, NMe), 4.10, 4.20 (1H, 2s, OH), 4.61, 4.70, (1H, 2s, CHC=O), 6.65-7.35 (5H, m, Ar-H), 7.65, 7.8 (1H, 2bs, N=CNH), 10.2 (1H, bs, NH indole).
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11. 1H NMR data for **16**: δ $CDCl_3$ -0.10 (9H, s, $SiMe_2$), 0.77-0.84 (2H, app.dd, OCH_2CH_2Si), 1.35-1.55 (1H, m, $CH_2CHH'CH_2$), 1.60-1.80 (1H, m, $CH_2CHH'CH_2$), 1.97-2.11 (2H, m, $CqCH_2CH_2$), 2.61 (1H, ddd, $ArCHH'$), 2.79-2.93 (1H, m, $ArCHH'$), 3.33-3.50 (2H, app. sextet, OCH_2CH_2Si), 3.67, 3.75 (2H, abq, $CqCH_2O$), 6.68, 6.80 (2H, 2d, Ar-H), 7.12 (1H, t, Ar-H), 7.63 (1H, bs, NH).
12. The coordinates for **2a** have been deposited at the Cambridge Crystallographic Data Centre.
13. The authors wish to acknowledge the support of the Analytical Sciences, Microbial Cell Sciences, and Microbial Metabolism and Biochemistry Departments of SmithKline Beecham Pharmaceuticals, Brockham Park.

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