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Chemical development of the vasopressin receptor 2 antagonist SR-121463*

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Abstract: A facile convergent total synthesis of the selective, potent, and orally active V_2 non-peptide antagonist, SR-121463, was developed by modification of the discovery route. One of the late intermediates, the sulfonyl chloride **1**, was synthesized from 3-hydroxybenzoic acid (**19**) by regioselective sulfonation, *O*-methylation and amidation in four steps. Another late intermediate, indolin-2-one **2,** was prepared from *p*-phenetidine (**8**) through the indolin-2-one **16**, where the cyclohexanone moiety of **27** was introduced into the active 3-methylene group of **16** by sequential transformation using methyl acrylate and KO*t*Bu. After formation of the cyclic ketal moiety of **13**, its ring-opening was achieved by using $NaBH_4$ in the presence of CCl_3COOH. The morpholino group in **2** was introduced in accordance with the discovery approach, starting from the 2-hydroxyethoxy derivative **14** through the tosyloxy derivative **15** with morpholine in a one-pot reaction. In this way, the indolin-2-one **2** was synthesized from **8** in six steps. Finally, acylation of the indolin-2-one **2** was achieved with the sulfonyl chloride **1** in the presence of KO*t*Bu in dimethyl sulfoxide (DMSO) at room temperature. This synthetic route proved to be applicable for the large-scale synthesis of SR-121463.

INTRODUCTION

The key elements of drug discovery and development are biological target selection and lead compound selection in the early pharmaceutical research, and preclinical and clinical evaluation of a drug candidate in the late pharmaceutical R&D activities (Fig. 1). Chemists play a significant role as medicinal chemists in the early stages, and as process chemists in the late stage of drug research. In 1999, at the

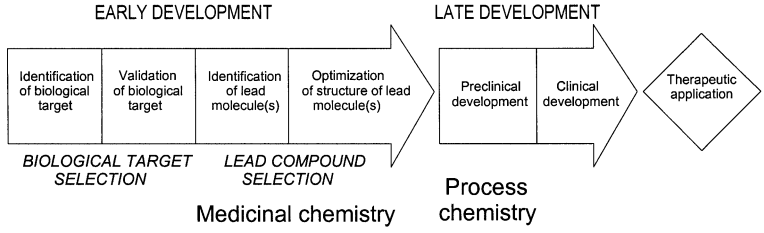

Fig. 1 Main activities in drug discovery and drug development.

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First Italian-Hungarian-Polish Joint Meeting on Medicinal Chemistry at Giardini-Naxos, Sicily, we discussed the content and applications of the means of medicinal chemistry in the case of prolyl endopeptidase inhibitors [1,2].

On this occasion, we discuss the next step, the process chemistry activities as the initial stages in the preclinical development of a drug candidate. We present here results on the process research of a non-peptide antagonist (SR-121463) of arginine vasopressin receptor 2.

ARGININE VASOPRESSIN RECEPTORS AND THEIR NON-PEPTIDE INHIBITORS

Arginine vasopressin (AVP) is a cyclic nonapeptide (Fig. 2) with distinct biological functions [3]. Its primary role involves regulation of the renal and cardiovascular functions [4]. To date, 3 subtypes of AVP receptors have been identified and cloned [5,6]: the V_1-vascular receptor [5], the V_2-renal receptor [6], and the V_{1b} or V_3-pituitary receptor [7,8]; however, their crystallographic structures remain to be established. They belong in the G protein-coupled superfamily [9]. Recent reports on AVP agonistic activity suggest the presence of an as yet uncharacterized new AVP receptor [10,11]. Depending on the second messenger involved, this could be classified as a V_{1c} or V_{2b} receptor.

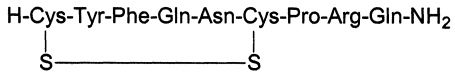


Fig. 2 Arginine vasopressin (AVP).

While potent and selective V_{1a} and V_2 non-peptide antagonists have been developed, there is still a need for potent and selective V_{1b} non-peptide antagonists. Potential therapeutic uses of AVP receptor antagonists include the blockade of V_1-vascular receptors in arterial hypertension, congestive heart failure (CHF), and peripheral vascular diseases; the blockade of V_2-renal receptors in the syndrome of inappropriate AVP secretion, CHF, liver cirrhosis, nephrotic syndrome, and any state of excessive retention of free water and subsequent hyponatremia; the blockade of V_{1b} (V_3)-pituitary receptors in adrenocorticotropin (ACTH)-secreting tumors [12].

The first selective non-peptide V_{1a} antagonist, OPC-21268, a tetrahydroquinolinone derivative, was developed by Otsuka Pharmaceuticals [13] (Fig. 3). Unfortunately, marked species differences have been reported; the affinity of OPC-21268 for the human V_{1a} receptors is rather weak [14,15], whereas high affinity for the rat liver receptor has been confirmed. An alternative non-peptide V_{1a} receptor ligand, SR-49059, an indoline derivative, was developed by Sanofi researchers [16]. This molecule displays high affinity, selectivity, and efficacy at V_{1a} receptors in human tissues where OPC-21268 is

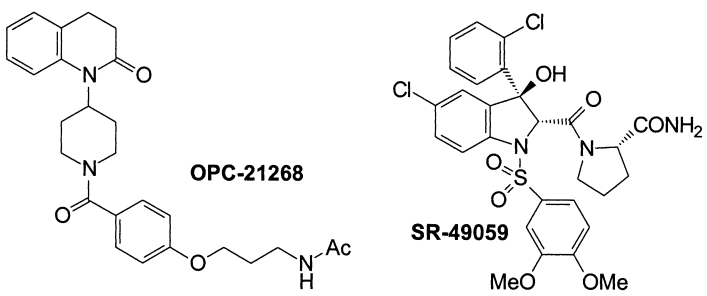


Fig. 3 Non-peptide inhibitors of AVP receptor 1a.

almost ineffective. SR-49059 has entered clinical trials for hypertension and CHF, and represents an important new pharmacological tool.

As yet, there has been no report on non-peptide V_{1b}-receptor antagonists, but very potent and selective V_2 non-peptide antagonists have been developed (Fig. 4), which are the congeners of previously discussed V_{1a} antagonists (Fig. 3). Otsuka Pharmaceuticals developed a benzazepine derivative, the orally bioavailable OPC-31260 [17,18], which proved to be active in humans [19]. The Sanofi group also reported an orally bioavailable V_2 antagonist, SR-121463 [20]. VPA-985 is another specific and selective V_2 antagonist, developed by Wyeth-Ayerst Research; it is currently being evaluated in clinical trials [21]. Yamanouchi Pharmaceutical also recently reported an orally effective, dual V_{1a}/V_2 receptor antagonist, YM-087. The V_2 receptor blockade is more pronounced than the V_{1a} receptor blockade [22,23].

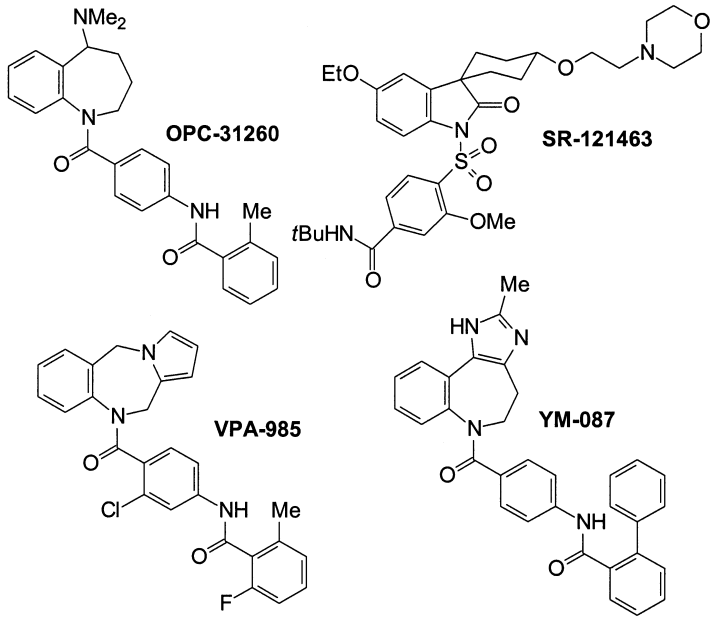


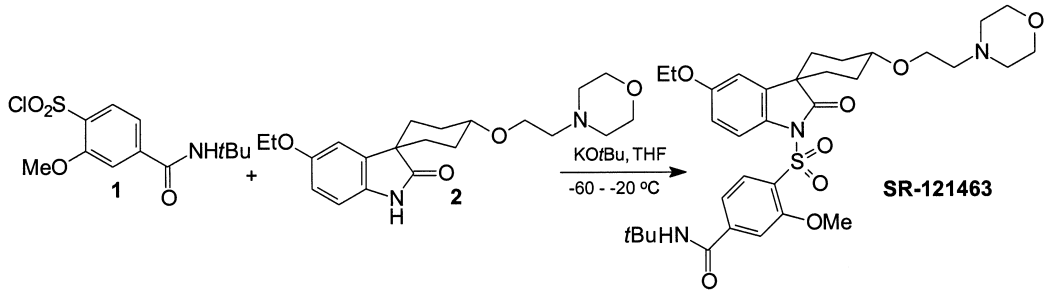
Fig. 4 Non-peptide inhibitors of AVP receptor 2.

The AVP V_2 receptor has been defined as the renal adenylate cyclase-coupled receptor involved in the antidiuretic effect of AVP [24]. AVP stimulation of the V_2 receptors on kidney collecting duct cells causes the migration of aquaporin 2 water channels to the cell surface, promoting water reuptake. The V_2 receptor inhibitors shut off cAMP and aquaporin 2 production, so that water is released as urine, with little effect on the urinary sodium and potassium excretion, which is at variance with classical natriuretic agents. The term "aquaretics" has been coined to describe this class of agents [25].

We present here an account of our results on the process research performed to develop a facile total synthesis of SR-121463 suitable for large-scale operation.

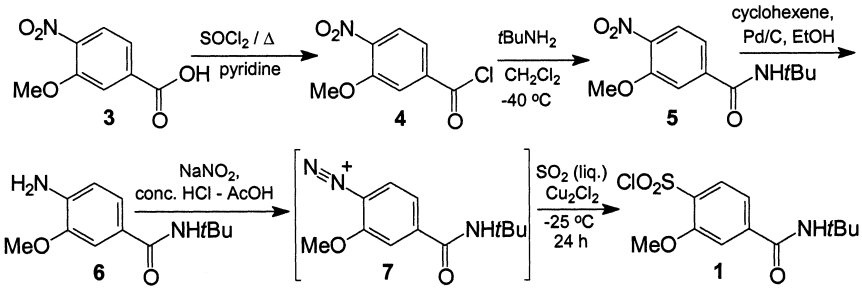
DISCOVERY ROUTE FOR THE SYNTHESIS OF SR-121463

The discovery route for synthesis of SR-121463 is depicted in Schemes 1–4 [26]. The final step in the synthesis involves the acylation of the N(1) nitrogen of the indolin-2-one **2** with the sulfonyl chloride **1** in tetrahydrofuran (THF) between –60 and –20 °C in the presence of KO*t*Bu to provide SR-121463 (Scheme 1).



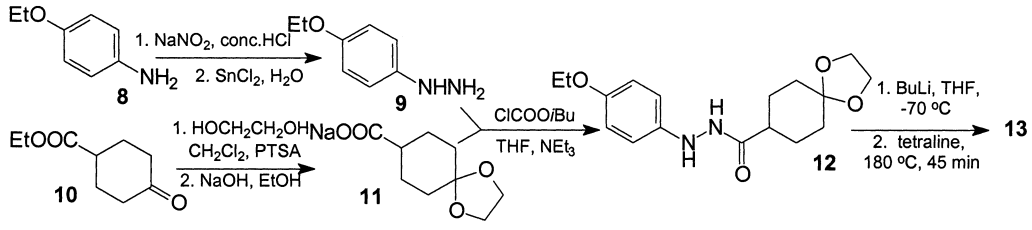
Scheme 1 Final step in the synthesis of SR-121463.

In the synthesis of the sulfonyl chloride **1,** medicinal chemists started from 3-methoxy-4-nitrobenzoic acid (**3**) (Scheme 2). First, the carboxylic acid chloride **4** was formed by treatment of **3** with $SOCl_2$, after which **4** was reacted with $tBuNH_2$ at –40 °C to give the benzamide **5**. The nitro group of the benzamide **5** was reduced to an amino group by a hydrogen-transfer reaction using cyclohexene over Pd/C as catalyst. The subsequent diazotization of *N*-(*tert*-butyl)-4-amino-3-methoxybenzamide (**6**) with $NaNO_2$ in acidic medium yielded the diazonium salt **7**. The diazonium moiety of **7** was replaced by a sulfonyl chloride group by treatment with liquid SO_2 at –25 °C, to afford **1**.



Scheme 2 Discovery route for the synthesis of the sulfonyl chloride **1**.

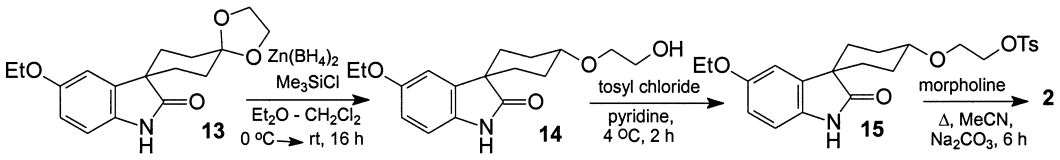
In the synthesis of the indolin-2-one **2,** medicinal chemists started from *p*-phenetidine (**8**), which was diazotized in concentrated HCl with $NaNO_2$, and the diazonium group was subsequently reduced to a hydrazine group with $SnCl_2$ (Scheme 3). The arylhydrazine **9** was reacted with a mixed anhydride, formed from the sodium cyclohexylcarboxylate derivative **11** with isobutyl chloroformate in THF in the presence of NEt_3. The sodium cyclohexylcarboxylate derivative **11** was prepared from the expensive ethyl 4-hydroxycyclohexylcarboxylate. Its oxidation with pyridinium chlorochromate on basic alumina in EtOAc afforded the cyclohexanone **10**, which was reacted with ethylene glycol in the presence of



Scheme 3 Discovery route for spiroindolin-2-one **13**.

p-toluene sulfonic acid (PTSA), followed by the hydrolysis of ester group with NaOH in EtOH to yield sodium salt **11**. Fischer indolization of the cyclohexylcarbohydrazide **12** in the Brunner reaction [27,28], with formation of the lithium salt of **12** with BuLi in THF at –70 °C, followed by heating of the lithium salt of **12** in tetraline at 180 °C, yielded 3-spiro(4,4-ethylenedioxycyclohexane)indolin-2-one **13**.

The cyclic ketal moiety of compound **13** was opened by treatment with $Zn(BH_4)_2$ in the presence of Me_3SiCl to afford a 85:15 mixture of *cis* **14** and *trans* (not shown) isomers of the 2-hydroxyethoxy derivative (Scheme 4). Pure **14** could be obtained by crystallization from toluene. The hydroxy group of the 2-hydroxyethoxy derivative **14** was acylated with tosyl chloride, and the tosyloxy group of **15**



Scheme 4 Discovery route for the indolin-2-one **2**.

was then replaced by a morpholino group by reaction with morpholine in the presence of Na_2CO_3 to yield the desired indolin-2-one **2**.

The main drawbacks of the discovery route are as follows:

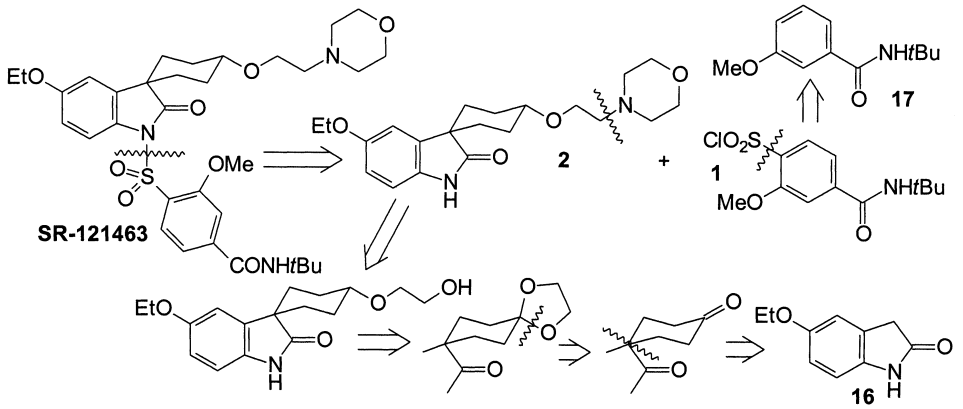
- introduction of the sulfonyl chloride group through the diazonium moiety of **7** with liquid SO_2
- preparation of the arylhydrazine **9** from *p*-phenetidine (**8**) through a diazonium salt and its reduction with $SnCl_2$
- use of the Brunner modification of Fischer indolization, lithium salt formation of **12** with BuLi at –70 °C, change of solvent for tetraline, and heating at 180 °C
- use of $Zn(BH_4)_2$, which is moisture and air-sensitive, and should be freshly prepared [29]
- starting from commercially unavailable 3-methoxy-4-nitrobenzoic acid (**3**) and the expensive ethyl 4-hydroxycyclohexylcarboxylate

These drawbacks make this approach unattractive for large-scale operation.

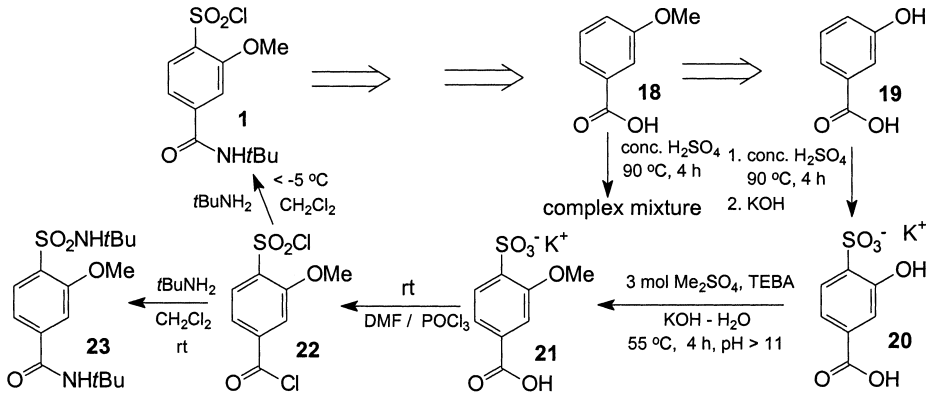
DEVELOPMENT ROUTE FOR SR-121463

After a retrosynthetic analysis of SR-121463 (Scheme 5), we decided to use a 3-methoxy- or 3-hydroxybenzoic acid derivative as starting material for the synthesis of building block **1**, and the 3-unsubstituted indolin-2-one **16** for the synthesis of building block **2**.

First, we attempted the sulfonation of 3-methoxybenzoic acid (**18**) with concentrated H_2SO_4, but unfortunately this led to a complex reaction mixture (Scheme 6). Next, we adapted the work of Shah [30], starting from 3-hydroxybenzoic acid (**19**), but concentrated H_2SO_4 was used instead of H_2SO_4 containing 3% SO_3. In this case, only the desired sulfonic acid was formed and isolated as its potassium salt **20**. The critical step was the regioselective methylation of **20**, which could be achieved in excellent yield under phase-transfer conditions, when the pH of the reaction mixture was maintained above 11 by the slow simultaneous addition of a KOH solution and Me_2SO_4. The diacyl chloride **22** was smoothly prepared from a potassium salt **21** with the Vielsmeier–Haack reagent at room temperature. When **22** was reacted with *t*$BuNH_2$ at room temperature, the diamide **23** was obtained. However,



Scheme 5 Retrosynthetic analysis of SR-121463.

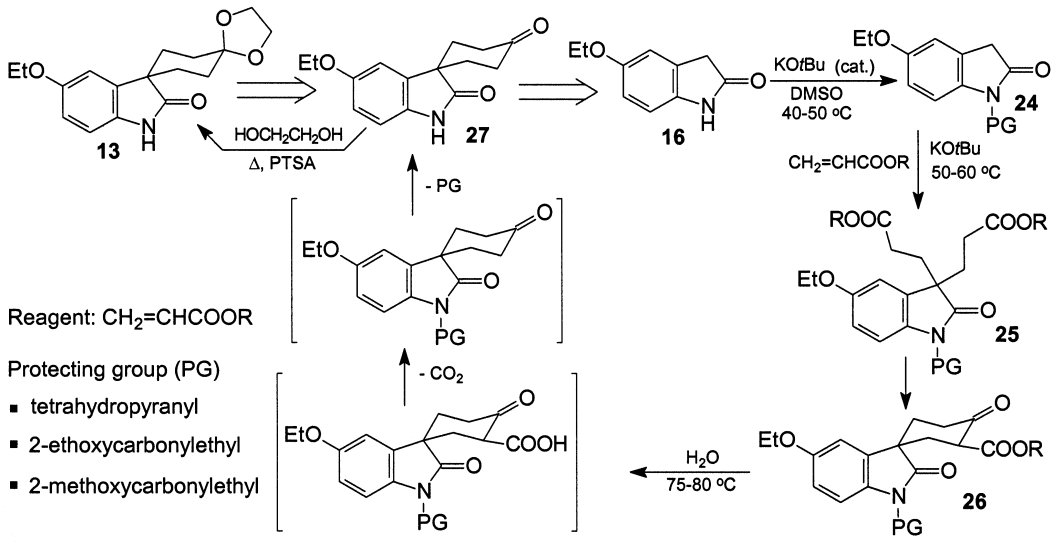


Scheme 6 Development route for the sulfonic acid **1.**

decrease of the reaction temperature to below –5 °C resulted in the regioselective amidation of **22** to provide exclusively the sulfonyl chloride **1**.

The indolin-2-one **16** was prepared by the method of Di Malta *et al*. [31]. Ethyl 2-chloro-2-(methylthio)-acetate, prepared *in situ* from ethyl 2-chloroacetate and Cl_2 in CH_2Cl_2 at –70 °C, was reacted with **8** in the presence of NEt_3, while the reaction temperature was allowed to increase from –70 °C to room temperature, to yield 5-ethoxy-3-(methylthio)indolin-2-one. Treatment of the 3-methylthio derivative with Raney Ni in *i*PrOH at 80 °C under nitrogen provided the 3-unsubstituted indolin-2-one **16**.

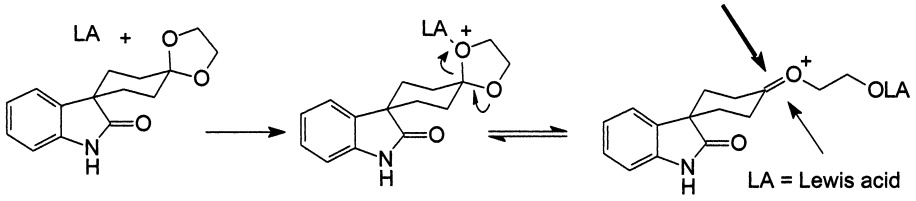
We set out to introduce the cyclohexanone moiety into the active 3-methylene group of **16** by the Michael addition [32] of alkyl acrylate, followed by the Dieckmann condensation [33] of the diester **25**, and then hydrolysis of the β-oxo ester **26** (Scheme 7). In the initial experiments, we used the acid-labile tetrahydropyranyl group [34] for protection of the NH in **16**. The overall yield of **27** was low (~20%), and accordingly we considered the use of alkyl acrylate not only as reagent, but also as protecting group. The alkoxycarbonylethyl protecting group could be eliminated by an E1cB mechanism [35]. The addition of ethyl acrylates was carried out in DMSO in the presence of KO*t*Bu. We isolated intermediates **24**–**26**, and the hydrolysis and deprotection were performed separately. The application of methyl



Scheme 7 Development route for the spiroindolin-2-one **13**.

acrylate gave a better yield than that with ethyl acrylate. Finally, we developed a sequential transformation [36] in which a 2-methoxy-carbonylethyl group was introduced into **16** at 40–50 °C with methyl acrylate in the presence of a catalytic amount of KO*t*Bu; the reaction temperature was then increased to 50–60 °C, and another portion of KO*t*Bu was added to the reaction mixture. The completion of the Michael addition and the subsequent Dieckmann condensation of the diester **25** were followed by means of thin-layer chromatography (TLC) investigations. After this, H_2O was added to the reaction mixture, and the hydrolytic process and deprotection started at 75–80 °C. This one-pot reaction afforded compound **27** a yield of over 60%. The reaction of **27** with ethylene glycol in the presence of PTSA furnished the spiroindolin-2-one **13**.

From this point, we applied the discovery route (Scheme 4), but we used $NaBH_3CN$ in the presence of $BF_3{\cdot}Et_2O$ instead of the $Zn(BH_4)_2$–Me_3SiCl system, and we obtained an 85:15 mixture of *cis* **14** and *trans* 2-hydroxyethyl derivatives. When we carried out this reduction on a 25 mol scale in a closed system, special attention was paid to destruction of the liberated HCN. The roles of the Lewis acids (e.g., BF_3) and Me_3SiCl in this reduction are the coordination of one of the oxygens of the ketal moiety, and the formation of a ring-chain tautomer. In the ring tautomer, (Scheme 8) the oxonium species is involved in the reduction. The formation of the *cis* and *trans* isomers is governed by steric factors. The Lewis acid could be replaced by proton, when a strong acid such as CF_3COOH or CCl_3COOH, was applied, and $NaBH_4$ could be used as reducing agent.



Scheme 8 Role of a Lewis acid in the ring opening of the dioxolane moiety.

We also introduced the morpholino group in a one-pot reaction. The hydroxy group in **14** was tosylated in pyridine, the reaction mixture was then diluted with EtOH and morpholine was added. After boiling for 1 h, the indolin-2-one **2** was obtained in good yield. Acylation of the indolin-2-one **2** with the sulfonyl chloride **1** was achieved at room temperature in the presence of KO*t*Bu, with DMSO used as solvent instead of THF.

The elaborated synthetic route was applied without difficulty in large-scale operations and provided SR-121463 in good quality, containing less than 0.2% of the *trans* isomer. The overall yield of the discovery route (~0.2%) was increased to 9%.

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