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Synthetic Studies toward Zoapatanol

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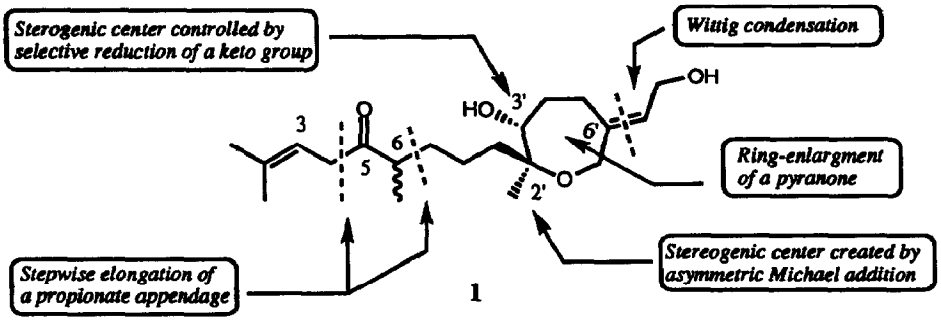
Abstract : Enantioselective elaboration of advanced intermediates in the synthesis of the anti-fertility agent zoapatanol 1, from pyranone (S)- 8, is described.

The aqueous extract of the leaves of the Mexican plant zoapatle (*Montanoa tomentosa*, Compositae) has been used in folk medicine by Mexican women to induce menses and labor and to regulate fertility. The predominant component responsible for the physiological activity of this extract has been identified as being the oxepane diterpenoid zoapatanol **1**[1].



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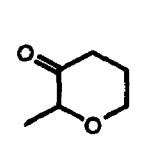
The purpose of the present paper is to report the enantioselective elaboration of advanced intermediates in the approach to **1**. Our synthetic plan, outlined in formula **1**, featured the general methodology for the stereocontrolled construction of stereogenic carbon centers we have reported a few years ago, based on the Michael-type addition of chiral imines to electrophilic alkenes[2]. It was our original hope that a concise, direct route to **1** might utilize chiral imine **6**, derived from oxepanone **5**. The latter compound was prepared in three steps, by ring-enlargment of pyranone **2**.[3] To attain this end, **2** was converted into silyl enol ether **3**[4] (TMSOTf / Et_3N, CH_2Cl_2) which, upon dibromocarbene addition (*t*BuOK / $CHBr_3$, hexane, -78 °C), followed by acidic treatment of the intermediary bicyclic adduct (1*N* HCl in THF, 2 h at 20 °C)[5], led to bromo-enone **4** (40 % overall yield from **2**). Catalytical reduction of **4** (5 bars of H_2, Pd/C, MeOH, $NaHCO_3$) finally gave oxepanone **5**

with a 56 % yield. Crude chiral imine **6**, prepared from **5** and *R*-(+)-1-phenylethylamine (60 °C, 24 h, cyclohexane, in the presence of a catalyst)[3], was then exposed to methyl acrylate (neat, 60 °C, 3 days)[2] leading, after hydrolytic work-up (20 % aqueous AcOH in THF), to desired Michael adduct (*S*)-7.[6] Unfortunately this adduct was obtained with a modest yield (25 % from **5**); furthermore the ee observed in this reaction was only 58 % (by comparing the optical rotations of 7[6] and of the enantiopure compound, resulting from the catalytical hydrogenation of **9**, *vide infra*).



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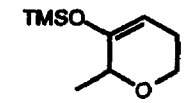

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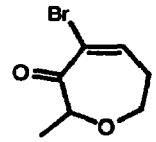

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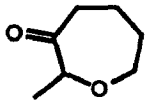

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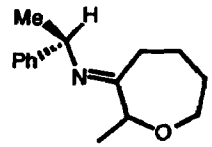

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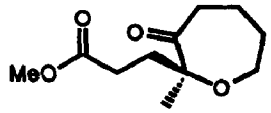

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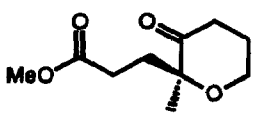
In order to improve the above results, an alternative route was devised, based on the ring-enlargment of enantiopure pyranone (*S*)-8[3] bearing the already controlled crucial stereogenic center at the α-position to the carbonyl group (C-2' center of zoapatanol **1**). Thus compound **8** was transformed in enantiopure (*S*)-7,[6] by a procedure in all points identical with conversion [**2** → **5**], *via* bromo-enone **9**.

In relation with the control of the stereogenic center at C-3' of zoapatanol **1**, reduction of the keto group of oxepanone **7** was next investigated, employing a variety of reagents. *Trans* pyrano-oxepane **10** and *cis* isomer **11**, resulting from the lactonization of the intermediary hydroxyesters, were directly formed in this reduction; these compounds were easily separated by chromatography on silica gel and unambiguously identified by ^{1}H NMR spectroscopy.[7] Although the *achiral* reducing agents ("*substrate-control*" conditions : the control of the newly created stereogenic center is determined by the intrinsic chirality of the substrate) furnished only modest selectivities, the use of B-chlorodiisopinocampheylboranes (Ipc_2BCl)[8] as *chiral* reagents ("*reagent-control*" conditions: the stereocontrol is mainly determined by the chirality of the reagent) allowed excellent stereoselectivities. However it should be pointed out that the *double diastereodifferentiation phenomenon* was observed with the latter reagents, (+)-Ipc_2BCl giving predominantly the desired *trans* derivative **10** with a 16:1 ratio (88 % yield), and (-)-Ipc_2BCl the *cis* isomer **11**, with a ratio of 50:1 (80 % yield).



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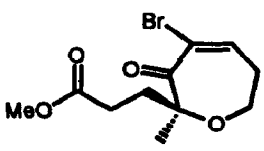

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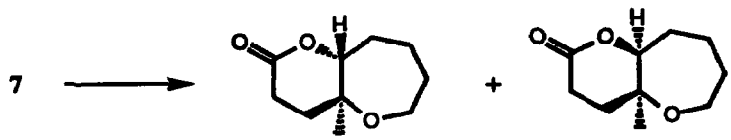
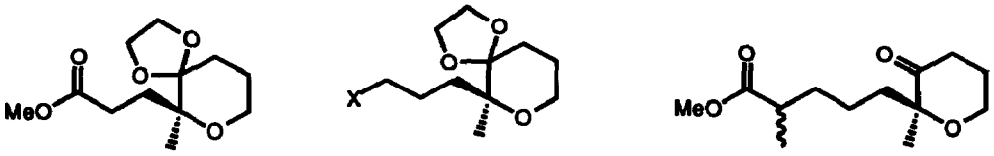


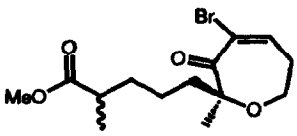
	10		11
$NaBH_4$ / EtOH (-40 °C → -20 °C)	1	:	3
$NaBH_4$ / $CeCl_3$ / EtOH (-20 °C → 20 °C)	1	:	2.5
H_2 (6 bars) / PtO_2 / MeOH-AcOH	1.5	:	1
$LiAlH(O^tBu)_3$ (THF, 20 °C)	2.8	:	1
(+)-Ipc_2BCl (neat, 20 °C)	16	:	1
(-)-Ipc_2BCl (neat, 20 °C)	1	:	50

Elongation of the propionate appendage of pyranone **8** was next undertaken, in connection with the construction of the dimethylnonenone side-chain of zoapatanol **1**. Considering the great sensitivity of the terminal part of this chain (β,γ-ethylenic ketone), and taking into account that an organometallic condensation, using 3-methyl-2-butenyllithium, on an α-methylpentanoic substituent at C-2' of **1** could complete this side-chain at the latest synthetic stages,[9] we decided to create such a substituent on **8**, by coupling the lithium dianion of propionic acid with iodide **13c** [**13c** → **14**]. For this purpose, the keto group of pyranone **8** was first protected (TMSOTf, $(TMSOCH_2)_2$, pyridine, 0 °C, 95 % yield)[10] and the resulting ketal-ester **12** transformed into alcohol **13a** (LAH, THF, 20 °C, quantitative). The latter compound was then converted into desired iodide **13c** by a two-step sequence, through tosylate **13b** (*i*: TsCl, pyridine; *ii* : NaI in refluxing acetone, 77 % overall yield). Condensation of the lithium dianion of propionic acid with this iodide (propionic acid, LDA, 0 °C), followed by acidic work-up and esterification with diazomethane finally led to pyranone-ester **14** (51 % overall yield), as a nearly equimolar mixture of diastereomers.



12 **13** **a** : X = OH; **b** : X = OTs; **c** : X = I **14**

Ring-enlargment of **14**, and subsequent functionalization of the resulting oxepanone at the carbon center in the γ-position to the keto group (C-6' center of zoapatanol **1**) were next examined. Thus **14** was transformed into bromo-enone **15**, with an overall yield of 65 %, by a protocol in all points identical with conversion [**2** → **4**]. Deconjugative reduction of this bromo-enone ($HPO(OEt)_2$, Et_3N, 20 °C)[11] then led to β,γ-enone **16** (66 % yield) which was epoxidized into **17** (H_2O_2 / Cl_3CCN, CH_2Cl_2, 0 °C, 67 % yield).[12]



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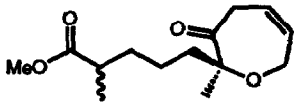

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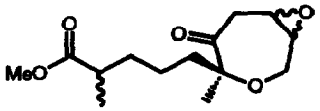

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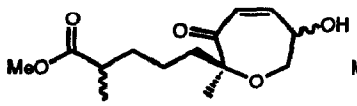
Treatment of **17** with DBU (toluene, 0 °C) gave allylic alcohol **18** (74 % yield). The double bond of **18** was reduced catalytically (H_2, Rh on carbon, AcOH, quantitative) and the resulting saturated alcohol was then oxidized with the Ley's reagent [13] (1 % tetra-*n*-propylammonium per-ruthenate, *N*-methyl morpholine *N*-oxide), giving oxepanedione **19**[14] (70 % yield). In relation with the introduction of the hydroxyethylidene function at C-6' of zoapatanol **1**, the addition of the Wittig reagent Ph_3P=CH-COOMe to dione **19** was next attempted (CH_2Cl_2, 40°C). As expected, this reaction was found to be highly chemoselective, since taking place exclusively on the *less* hindered keto group of **19**, thereby delivering with a 80 % yield the desired adduct **20**[15], as an equimolar mixture of olefinic isomers.



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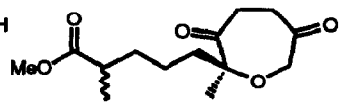

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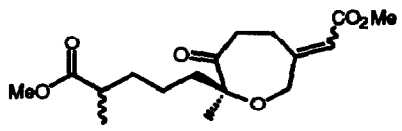

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The main problems encountered in the conversion of (*S*)-**8** into zoapatanol **1** have thus been efficiently solved. Work is pursued in our laboratory to complete the synthesis of **1** and of related molecules.

References and Notes

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6- Enantiopure (*S*)-**7** : $[\alpha]_D^{20}$ -29.8 (c = 5.4, MeOH).

7- ^{1}H NMR spectra of **10** and **11** (200 MHz, $CDCl_3$) δ: **10** : 4.18 (dd, J = 10.9, 3.3 Hz, 1H); **11** : 4.30 (dd, J = 7.4, 0.6 Hz, 1H).

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14- **19** : oil; IR (neat, cm^{-1}): 1730, 1720; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (d, J = 7.0 Hz, 3H) 1.32 (s, 3H) 1.23-1.46 (m, 2H) 1.58-1.77 (m, 4H) 2.42 (m, 1H) 2.51-2.74 (m, 2H) 2.82-2.94 (m, 1H) 2.94-3.10 (m, 1H) 3.67 (s, 3H) 4.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.1, 19.7 and 19.8 (diastereomeric signals), 20.6, 33.8, 34.4, 36.6 37.2, 39.2, 51.5, 71.6, 86.7, 176.9, 210.3, 213.9.

15- **20** : oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.2 (d, 3H, J = 6 Hz) 1.28 (s, 3H) 1.2-1.5 (m, 2H) 1.53-1.76 (m, 4H) 2.46 (m, 1H) 2.51-3.06 (m, 4H) 3.67, 3.69 and 3.72 (3 s, 6H, isomeric signals) 4.09 and 4.72 (2 s, 2H, isomeric signals) 5.78 (s, 1H).

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