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An Enantioselective Total Synthesis of (+)- and (−)-Saudin. Determination of the Absolute Configuration

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Saudin (**1**) was isolated from *Clutya Richardiana* in 1985[1] and has been shown to possess in vivo noninsulin dependent hypoglycemic activity.[2] The highly oxidatively modified labdane diterpene presents a compact caged bis-ketal skeleton with five contiguous stereogenic centers, three of which are quaternary or fully substituted. Several approaches,[3] including a concise total synthesis of (±)-saudin,[4] have been reported.

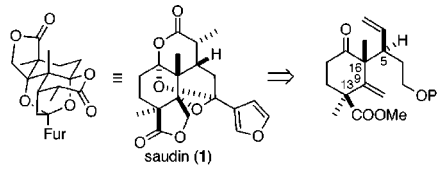
Herein we report the first enantioselective total synthesis of (+)- and (−)-saudin and the determination of its absolute configuration. The core of our synthetic strategy is a Lewis acid mediated stereoselective Claisen rearrangement to establish the correct relative stereochemistry between the two quaternary centers (C_{13} and C_{16}) as well as the required functionalization for further elaboration (Scheme 1).

Enone (−)-**6** was obtained from (*S*)-α-methylbenzyl carbamate **2** by Michael addition to ethyl vinyl ketone catalyzed by $ZnCl_2$ and aldol-dehydration of the resulting diketone **3**, which afforded (−)-**4** with high regioselectivity (18:1). After saponification and reesterification, (−)-**6** was isolated in 95% ee and 50% yield overall from ethyl 2-methyl acetoacetate (Scheme 2).[5] Derivatives **3**−**6** are known in the literature only in racemic form[6] but their analogues, obtained in a similar way using methyl vinyl ketone as the Michael aceptor, are described in optically pure form[5a,7] and the sense of the chiral induction is well established.[8] Furthermore, we have corroborated the absolute configuration of (−)-**4** at C_{13} by transformation of known (+)-**7**[9] into (−)-**4**.

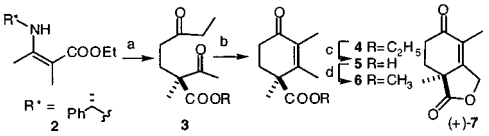
O-alkylation of the thermodynamic enolate prepared from **6** with allylic triflate **8** (prepared in 3 steps from the TBDPS ether of 3-butyn-1-ol) afforded Claisen rearrangement precursor **9**.[9b] Thermal Claisen rearrangement of **9** at 90 °C afforded a mixture of **10** and **11** (4:1) in which the undesired stereoisomer **10** predominated. This stereochemical outcome can be rationalized via a preferred chairlike transition state **12** (Figure 1) in which rearrangement occurs from the face of the half-chair cyclic enol ether ring allowing stereoelectronically favored axial bond formation at the ring stereogenic center.

To overcome this preference, we reasoned it would be necessary to induce a conformational change in the cyclohexenol ring. Reaction via a boatlike conformation would then allow stereoelectronically favored axial bond formation from the α face affording the required stereoisomer **11**. We chose to accomplish this using a bidentate Lewis acid promoter. Gratifyingly, treatment of **9** at −65 °C with excess $TiCl_4$, in the presence of Me_3Al as proton scavenger afforded adducts **10** and **11** (1:10), where **11** was now the major product, along with ca. 10% of **6** (Scheme 3).[10] The reversal in facial selectivity can be rationalized by invoking bidentate coordination by Ti(IV) of both the oxygen of the vinyl ether and the ester enforcing the boatlike conformation **13** in which rearrangement

Scheme 1



Scheme 2



[a] Ethyl vinyl ketone, PhMe, 50 °C; then aqueous HCl, room temperature. [b] Pyrrolidine, AcOH, PhMe, Δ (62% from 2-methyl ethylacetoacetate). [c] Aqueous KOH, MeOH, reflux. [d] K_2CO_3, $(CH_3)_2SO_4$, acetone, Δ (80% from **4**).

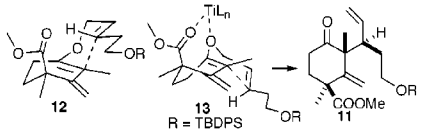
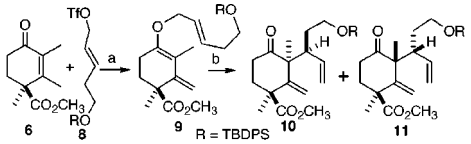


Figure 1. Transition states for the Claisen rearrangement.

Scheme 3



[a] KHMDS, THF−HMPA −78 °C to room temperature; then **8**, −78 °C (65%). [b] $TiCl_4$, Me_3Al, 4 Å MS, CH_2Cl_2, −65 °C (65%).

takes place via the chairlike transition state preferentially axial on the less hindered α face (Figure 1).[11]

Deprotection of silyl ether **11** with TBAF resulted in spontaneous formation of a mixture of hemiketals (∼1:1), which were directly converted to a single methyl ketal **14**. Hydroboration with 9-BBN occurred exclusively at the less hindered, monosubstituted olefin and the resulting primary alcohol **15** was efficiently converted to carboxylic acid **16**.[12]

Acid **16** was epoxidized with *m*CPBA to afford a single diastereomeric epoxy lactone **17** after acidic workup. Addition of 3-lithiofuran[13] to δ lactone **17** exhibited complete chemoselectivity affording only keto alcohol **18** (Scheme 4), as the other potentially electrophilic sites are apparently too hindered or unreactive to be competitive. Hydroxy ketone **18** was directly acetylated affording **19** in 81% overall yield (Scheme 4).

The C_9 tertiary oxygen center was installed by Lewis acid promoted opening of epoxide **19** with inversion via nucleophilic participation of the side chain ketone carbonyl followed by ring

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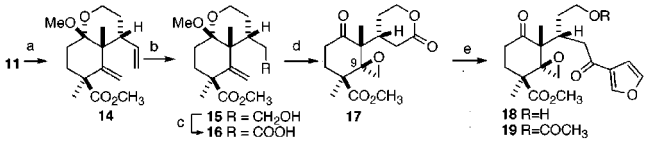
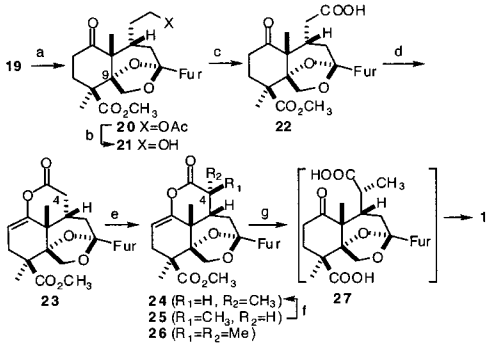
Scheme 4



[a] TBAF, AcOH, THF, room temperature, then TsOH, $CH(OMe)_3$, MeOH, room temperature. [b] 9-BBN, THF, reflux; then $NaBO_3$, H_2O, room temperature (87% from **11**). [c] DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −60 to 0 °C, then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, room temperature. [d] *m*CPBA, $NaHCO_3$, CH_2Cl_2, room temperature, then aqueous HCl, THF, room temperature (73% from **15**). [e] 3-Tributylstannyl furan, n-BuLi, THF, −78 °C, then Ac_2O, DMAP, py, CH_2Cl_2, room temperature (81% from **17**).

Scheme 5



[a] $BF_3{\cdot}Et_2O$, CH_3CN, room temperature (90%). [b] K_2CO_3, MeOH, H_2O, 0 °C. [c] DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −60 to 0 °C, then $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, room temperature. [d] NaOAc, $(CF_3CO)_2O$, CH_2Cl_2, room temperature (67% from **19**). [e] LiTMP, THF, −78 °C, then HMPA, MeI, −50 °C (75% of **24**/**25**). [f] LDA, THF, 0 °C (88%/70% combined of **24** from **23**). [g] 2 N aqueous KOH, reflux, then TMSOTf, $C_2H_4Cl_2$, room temperature (70% from **24**).

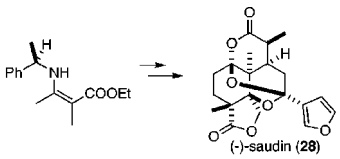
closure to bicyclic ketal **20**.[14] After saponification of acetate **20**, the resulting alcohol **21** was oxidized to carboxylic acid **22** (Scheme 5). Direct conversion of **21** to **22** could also be performed with catalytic TEMPO−NaOCl using $NaClO_2$ as co-oxidant,[15] but the yield was lower (65%) owing to concomitant oxidation of the furan ring.

Introduction of the C_4 secondary methyl group was initiated by conversion of acid **22** to the crystalline enol lactone **23** via the mixed trifluoroacetic anhydride (Scheme 5).[16] When LDA was employed as base, deprotonation of **23** and addition of CH_3I led to **24** and **25** in variable ratio and yield depending upon reaction conditions. Unreacted **23** along with significant amounts of dialkylated **26** were obtained even when an excess of base was used. It seemed likely that these difficulties resulted from proton exchange between **24** and **25** and the enolate derived from **23** perhaps facilitated by diisopropylamine.[17]

Fortunately, deprotonation of enol lactone **23** with the hindered strong base Li-TMP then addition of HMPA and CH_3I afforded monoalkylated products **24** and **25** (1:1.5) and only traces of **26**. Methyl diastereomers **24** and **25** were separated by chromatography and the axial stereoisomer **25** was equilibrated to **24** by treatment with a substoichiometric amount of LDA affording **24** in a combined 70% yield.

Although attempts to assemble the bis ketal system from **22** were unsuccessful, conversion of **24** to the bis ketal system occurred smoothly by hydrolysis of **24** followed by treatment of the resulting bis carboxylic acid **27** with TMSOTf[18] affording (+)-**1** in 70% yield (Scheme 5). The spectroscopic properties of (+)-**1** were identical with those of an authentic sample of natural (−)-saudin, except for the sign of the optical rotation: $[\alpha]_D^{25}$ +14 (*c* 0.460, $CHCl_3$), including melting point (mp 204−206 °C). Thus, the absolute configuration of natural (−)-saudin can finally be assigned as **28** as shown in Scheme 6.

Scheme 6



Using (*R*)-(+)-α-methylbenzylamine as the chiral auxiliary, we then employed the above-described sequence to achieve the first enantioselective total synthesis of (−)-saudin (**28**). Synthetic (−)-saudin (**28**) has $[\alpha]_D^{25}$ −14 (*c* 0.460, $CHCl_3$) and spectroscopic properties identical with those of the natural product.[1]

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Supporting Information Available: Experimental procedures, analytical data, and copies of ^{1}H NMR spectra for intermediates **9**, **11**, **14**, **16**, **17**, **19**, **20**, **23**, **24**, and synthetic (+)-**1** and natural (−)-**28** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Oxidation of **15** to **16** was also done in one step (75% yield) by using PDC under standard conditions. We prefer the former sequence since no purification is necessary and use of heavy metals is avoided.
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