Natural Product Synthesis

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A General Strategy for Construction of Both 2,6-*cis*- and 2,6-*trans*-Disubstituted Tetrahydropyrans: Substrate-Controlled Asymmetric Total Synthesis of (+)-Scanlonenyne**

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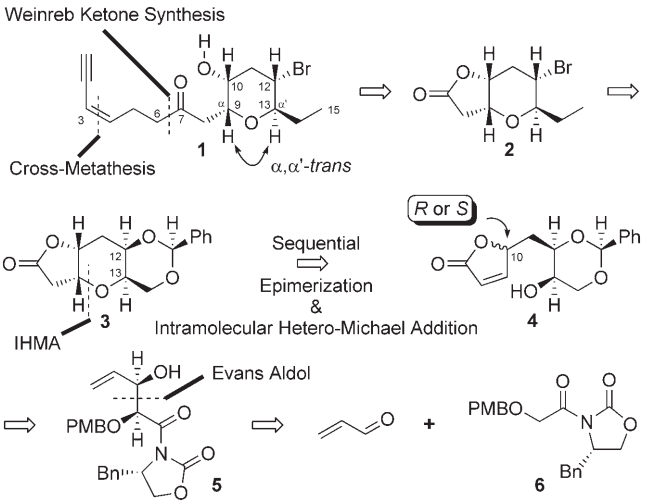
Functionalized 2,6-disubstituted tetrahydropyrans constitute key structural features of a large number of biologically active natural products.[1,2] We report herein a highly stereoselective general strategy for the synthesis of both 2,6-*cis*-disubstituted (α,α′-*cis*) and 2,6-*trans*-disubstituted (α,α′-*trans*) tetrahydropyrans on the basis of a novel sequential epimerization and intramolecular hetero-Michael addition of a hydroxybutenolide.[3] To illustrate the potential of this methodology, the first asymmetric total synthesis of (+)-scanlonenyne (**1**), a halogenated α,α′-*trans*-tetrahydropyranoid marine natural product, has been accomplished in a completely substrate-controlled fashion.

(+)-Scanlonenyne (**1**; see Scheme 1) was isolated by Suzuki and co-workers from the red alga *Laurencia obtusa* collected near Scanlon's Island, off the western coast of Ireland.[4] The constitution and relative stereochemistry of scanlonenyne were established on the basis of an extensive NMR spectroscopic study.[4] However, the absolute configuration, as well as the biological activity, of the pyranoid marine natural product could not be investigated due to the compound's lability.[4] Scanlonenyne represents the first halogenated C_{15} acetogenin with a ketonic functionality at the C7 position from a *Laurencia* species. The key structural features of this unique and unstable natural product that need to be addressed in a synthesis include 1) the α,α′-*trans*-disubstituted tetrahydropyran ring with four stereogenic centers, 2) the secondary bromine functionality, which must be incorporated in a stereoselective fashion, and 3) the C9 side chain, which possesses both a sensitive β-alkoxyketone moiety and a *Z*-enyne unit.

As shown in Scheme 1, we envisioned that (+)-scanlonenyne (**1**) could be elaborated from bicyclic bromo-γ-lactone **2**, which contains all four stereocenters of the natural product,



Scheme 1. Retrosynthetic plan for (+)-scanlonenyne (**1**). Bn: benzyl; IHMA: intramolecular hetero-Michael addition; PMB: *p*-methoxybenzyl.

by a Weinreb ketone synthesis/cross-metathesis strategy. The requisite bromo-γ-lactone **2** could, in turn, be prepared from key tricyclic intermediate **3** by a one-carbon homologation of the C13 side chain and bromination with inversion of configuration at the C12 position. However, the stereoselective introduction of the bromine substituent,[5] which is known to be particularly challenging, and the projected one-carbon extension[6] would be of considerable concern. Furthermore, we were intrigued by the possibility of securing the desired tricyclic α,α′-*trans*-disubstituted pyranolactone **3** by a sequential epimerization and intramolecular hetero-Michael addition of hydroxybutenolide **4**, irrespective of its configuration at the C10 position (see below). Further analysis suggested that IHMA substrate **4** should be readily accessible from the Evans *syn*-aldol adduct **5** of known glycolate oxazolidinone **6** with acrolein.

To commence the synthesis, an aldol reaction[7] of the dibutylboron enolate derived from the readily available

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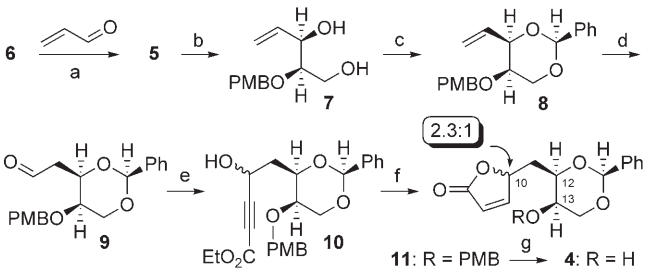
glycolate oxazolidinone **6**[8] with acrolein furnished the corresponding *syn*-aldol adduct **5** (62%, 91% based on recovered starting material (BRSM), d.r. 96:4 determined by ^{1}H NMR analysis; Scheme 2); this enabled the relative and

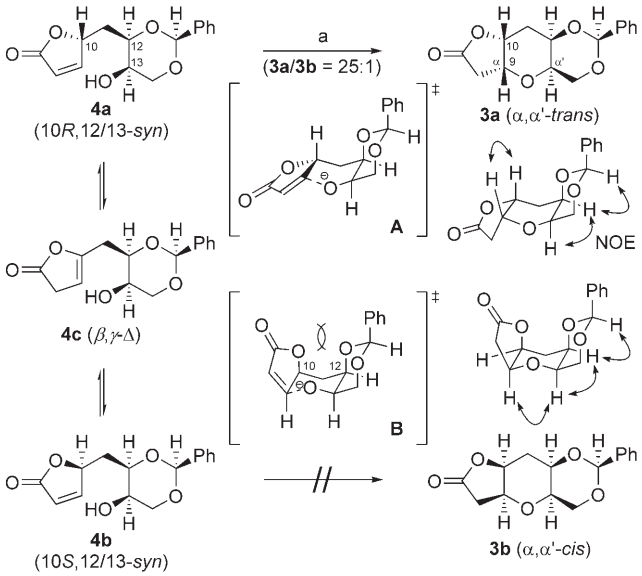


Scheme 2. Preparation of IHMA substrate **4**: a) 1. *n*Bu_2BOTf, Et_3N, CH_2Cl_2, −78→−40°C, 30 min; 2. acrolein, −78→0°C, 2 h, 62% (91% BRSM); b) $NaBH_4$, THF/H_2O (3:1), room temperature, 2 h; c) PhCH(OMe)$_2$, PTSA, CH_2Cl_2, room temperature, 36 h, 72% (2 steps); d) $PdCl_2$, CuCl, O_2, DMF/H_2O (7:1), room temperature, 6 h, 91%; e) ethyl propiolate, LDA, THF, −78→−30°C, 2 h, 87%; f) 1. H_2, Lindlar catalyst, EtOAc/pyridine (20:1), room temperature, 1.5 h; 2. silica gel, overnight, 97%; g) DDQ, CH_2Cl_2/buffer solution (pH 7.0; 9:1), room temperature, 1.5 h, 93%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, PTSA = *p*-toluenesulfonic acid, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

absolute stereochemistry at the C12/C13 positions of IHMA substrate **4** to be established. Reductive cleavage of the chiral auxiliary in **5**, followed by protection of the resulting diol **7** as the benzylidene acetal, provided cyclic acetal **8** in 72% yield for the 2 steps after isolation. We were pleased to find that a highly regioselective Wacker reaction[9,10] of monosubstituted terminal alkene **8** produced the desired aldehyde **9** in excellent yield (91%).[11] Addition of the lithium anion of ethyl propiolate to aldehyde **9**, followed by semihydrogenation of the resulting acetylenic ester **10** with Lindlar catalyst, gave rise directly to the desired butenolide **11** (84%, 2 steps). Oxidative cleavage of the PMB group in **11** by the Yonemitsu method[12] then afforded key intramolecular hetero-Michael precursor **4** as a 2.3:1 diastereomeric mixture at the C10 position in 93% yield. The configuration of the major isomer at the C10 position was determined to be *S* by X-ray crystallography (see the Supporting Information).[13]

Having developed a concise synthetic route to the key substrate for the intramolecular conjugate addition, we were delighted to find that, upon exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane, the 2.3:1 mixture of hydroxybutenolides **4** furnished the desired γ-lactone **3a** in 76% yield with 25:1 α,α′-*trans*:-*cis* selectivity. This sequential epimerization and IHMA process, which we believe proceeds through the intermediacy of β,γ-unsaturated butenolide isomer **4c**, establishes the configuration at the C9 and C10 positions in a single operation (Scheme 3).[14,15]

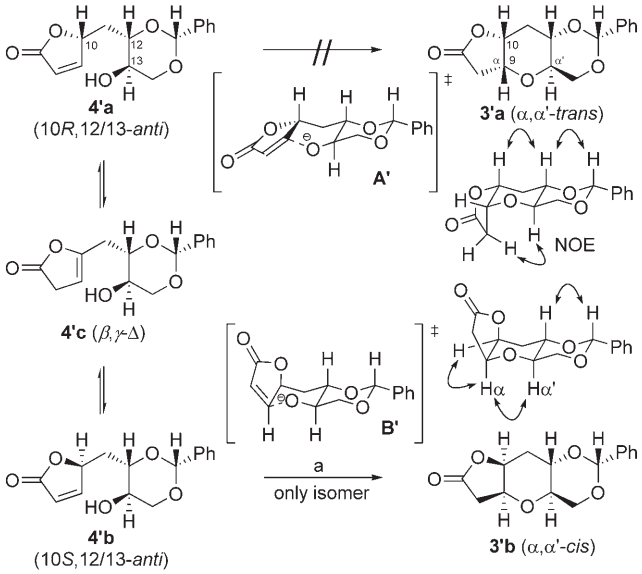
The observed stereochemical outcome can be rationalized by considering that the internal hetero-Michael addition of 10*R* isomer **4a** via boat-like transition state **A** proceeds faster than that of 10*S* isomer **4b**. Chair-like transition state **B** for **4b** suffers unfavorable nonbonding interactions between the two



Scheme 3. IHMA of C12/C13-*syn*-hydroxybutenolides **4**: a) DBU (2 equiv), CH_2Cl_2 (0.005 M), 34°C, 24 h, 76% (87% BRSM).

diaxial substituents at the C10 and C12 positions (as indicated in Scheme 3). The relative configuration of the newly generated stereocenters of tricyclic γ-lactone **3a** was assigned by NOESY studies and was further verified by single-crystal X-ray analysis (see the Supporting Information).[13] The X-ray crystallographic studies revealed that the tetrahydropyran ring of **3a** assumes a twist-boat conformation.

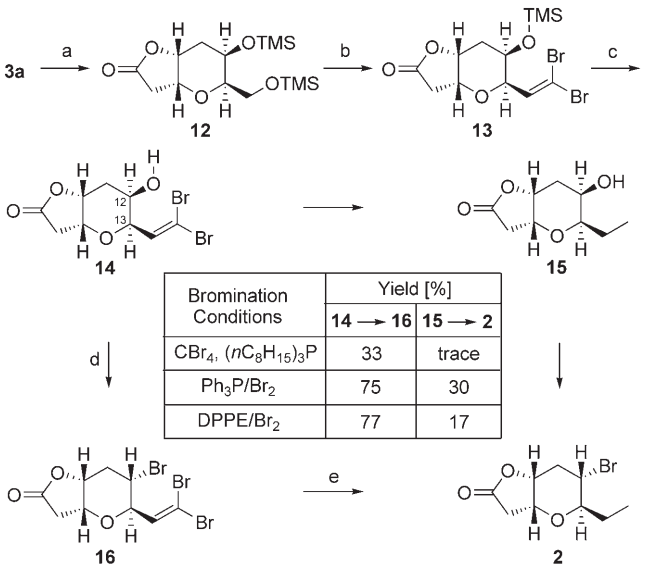
It is worth mentioning at this point that, in contrast to the results with C12/C13-*syn*-hydroxybutenolides **4**, intramolecular hetero-Michael addition of a 1:1 mixture of C12/C13-*anti*-hydroxybutenolides **4′** under comparable conditions produced α,α′-*cis*-pyrano-γ-lactone **3′b** as the sole product in 88% yield (Scheme 4).[14,16] The preferred chair-like



Scheme 4. IHMA of C12/C13-*anti*-hydroxybutenolides **4′**: a) DBU (2 equiv), CH_2Cl_2 (0.005 M), 24°C, 24 h, 88%.

transition-state geometry **B′**, which is devoid of the aforementioned destabilizing interactions in **B**, led to the formation of α,α′-*cis*-pyrano-γ-lactone **3′b**. The NOE interactions between Hα and Hα′ in **3′b** were consistent with a *cis* orientation.

With the synthesis of tricyclic α,α′-*trans*-lactone **3a** accomplished, we focused our attention on its conversion into key bromo-γ-lactone intermediate **2** (Scheme 5). As we



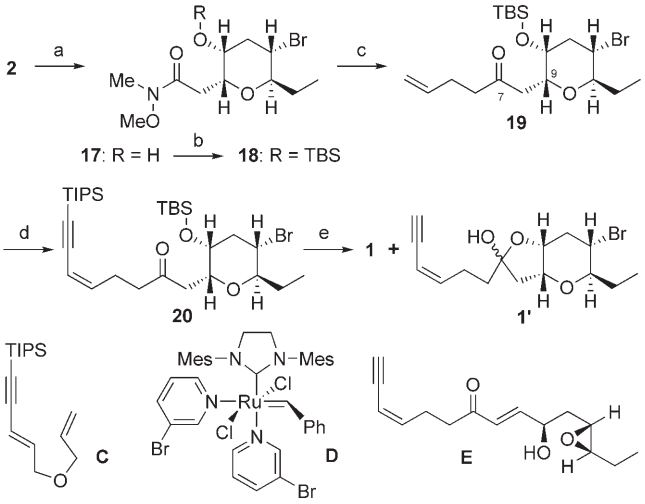
Bromination Conditions	Yield [%]	
	14 → 16	15 → 2
CBr_4, $(nC_8H_{15})_3P$	33	trace
Ph_3P/Br_2	75	30
DPPE/Br_2	77	17

Scheme 5. Synthesis of key bromo-γ-lactone **2**: a) 1. H_2, $Pd(OH)_2$, THF, room temperature, 2 h; 2. hexamethyldisilazane, imidazole, 60 °C, 2 h; b) 1. CrO_3, pyridine, CH_2Cl_2, room temperature, 1 h; 2. CBr_4, Ph_3P, room temperature, 10 min; c) PPTS, MeOH, room temperature, 10 min, 64% from **3a**; d) DPPE/Br_2, CH_2Cl_2/toluene (2:1), 70 °C, 6 h, 77%; e) H_2, 10% Pd/C, EtOAc, room temperature, 1 h, 93%. DPPE = 1,2-bis(diphenylphosphino)ethane, PPTS = pyridinium *p*-toluenesulfonate, TMS = trimethylsilyl.

initially feared, the requisite one-carbon homologation at the C13 position in the presence of the γ-lactone functionality proved to be problematic. However, we were able to devise an alternative synthetic sequence for this purpose by taking advantage of 1) the highly efficient transformation of an aldehyde function to the corresponding 1,1-dibromoalkene under the mild conditions of Corey and Fuchs[17] and 2) the ready hydrogenolysis of a carbon–halogen bond by using a palladium catalyst. Thus, removal of the benzylidene protecting group in **3a** by hydrogenolysis with Pearlman's catalyst,[18] followed by protection of the resulting diol with hexamethyldisilazane in a one-pot procedure, afforded bis-TMS ether **12**. A novel one-pot chemoselective desilative Collins oxidation/Corey–Fuchs olefination of the unstable bis-TMS ether **12** led to 1,1-dibromoalkenyl alcohol **14** after removal of the TMS group in intermediate **13**.[19] Experimentally, alcohol **14** could be prepared in excellent overall yield from **3a** (64%) without purification of intermediates.

Exposure of 1,1-dibromoalkenyl alcohol **14** to H_2/Pd then gave the requisite 13-ethyl alcohol **15**, ready for the crucial bromination. As anticipated, however, bromination of alcohol **15** with inversion of configuration turned out to be a significant challenge. After extensive experimentation, we made the unanticipated observation that **14** is a far better substrate for the bromination than **15** (Scheme 5).[20] Thus, exposure of **14** to DPPE/Br_2[21] furnished the corresponding bromide **16** in good yield (77% for **14** versus 17% for **15**). Finally, we were pleased to find that chemoselective hydrogenolysis of the vinylic dibromide moieties in tribromide **16** in the presence of the C12 alkyl bromide function, followed by hydrogenation of the resulting olefin, delivered key bromo-γ-lactone **2** in excellent yield (93%). The structure of **2** was firmly established by X-ray crystallography.[13]

With key bromo-γ-lactone **2** in hand, we proceeded to address the assembly of the C9 side chain by sequential installation of the β-alkoxyketone and the *Z*-enyne moieties (Scheme 6). It should be emphasized at this point that



Scheme 6. Completion of the synthesis of (+)-scanlonenyne (**1**): a) MeONHMe·HCl, Me_2AlCl, CH_2Cl_2, room temperature, 50 min, 95%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −30 °C, 10 min, 90%; c) $H_2C{=}CH{-}(CH_2)_2MgBr$, THF, room temperature, 40 min, 93%; d) enyne **C**, Grubbs catalyst **D**, benzene, 70 °C, 6 h, 50% (83% BRSM), *Z*/*E* = 5:1; e) TBAF, THF, −30 °C, 30 min, 77%. Mes = 2,4,6-trimethylphenyl, TBS = *tert*-butyldimethylsilyl, TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.

introduction of a ketone function at the C7 position renders the tetrahydropyran ring susceptible to rupture by a retro-Michael reaction. With this potential problem in mind, exposure of bromo-γ-lactone **2** to Me_2AlCl/MeONHMe·HCl by using the Shimizu–Nakata modification of the Weinreb protocol,[22] and subsequent silylation of the resulting γ-hydroxy-*N*-methoxy-*N*-methylamide **17** with TBSOTf, furnished TBS-protected Weinreb amide **18** in good yield (86%, 2 steps). Gratifyingly, treatment of Weinreb amide **18** with butenylmagnesium bromide provided the desired β-alkoxyketone **19** in excellent yield (93%).[23]

To complete the synthesis, we believed that our recently reported modification of the cross-metathesis protocol of Lee and co-workers[24] would be ideal for incorporation of the *Z*-enyne unit in the presence of the sensitive β-alkoxyketone moiety. We were pleased to find that, upon exposure to enyne **C** and Grubbs catalyst **D**, β-alkoxyketoalkene **19** delivered

the desired *Z* enyne **20** as a 5:1 mixture of *Z* and *E* isomers in 50% yield. Finally, the removal of both silyl groups in **20** by treatment with TBAF at low temperature yielded (+)-scanlonenyne (**1**) in 77% yield. It is interesting to note that treatment of enyne **20** with TBAF at room temperature produced epoxide **E** as the major product from the aforementioned retro-Michael process. The spectral and optical rotation data of our synthetic material were in good agreement with those of the natural product. However, closer examination of the proton and carbon NMR spectra of both the natural and synthetic materials revealed the presence of a small amount of inseparable substances, probably a diastereomeric mixture of hemiketals **1′** in equilibrium with the hydroxyketo form **1**.

In summary, the first asymmetric total synthesis of (+)-scanlonenyne (**1**) has been achieved in 18 steps in 9% overall yield from readily available glycolate oxazolidinone **6** and acrolein. Our completely substrate-controlled synthesis of this labile C_{15} acetogenin features a number of stereo-, regio-, and chemoselective transformations including 1) a novel sequential epimerization and intramolecular hetero-Michael addition of a hydroxybutenolide for construction of both the α,α′-*cis*- and α,α′-*trans*-pyranolactones, 2) a novel highly efficient one-carbon homologation/bromination strategy, and 3) a Weinreb ketone synthesis/cross-metathesis protocol for the elaboration of the sensitive C9 side-chain appendage. In addition, the present synthesis establishes the absolute configuration of the natural product.

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[14] See the Supporting Information for the optimized molecular geometries of **3a**, **3b**, **3′a**, and **3′b**. The global minimum conformations (Spartan06, MM2 force field, Monte Carlo conformational search) were further optimized by density functional theory (B3LYP) at the 6-31G* level (Gaussian03, D02 version); P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627. Note that the phenyl substituent has been replaced by a methyl substituent to expedite the B3LYP/6-31G* optimizations. The calculation showed that the ethylidene derivatives of **3a** and **3′b** were more stable than those of **3b** and **3′a** by 0.6 and 3.7 kcal mol^{-1}, respectively.

[15] a) Separation of the 10*R* and 10*S* isomers and subjection of each isomer to the IHMA conditions gave roughly the same result. b) The minor α,α′-*cis* isomer **3b** did not equilibrate to the corresponding *trans* isomer **3a** under the reaction conditions.

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