Toward the Development of a General Chiral Auxiliary. A Remarkable, Highly Diastereoselective, Auxiliary-Mediated Substitution: Application to an Enantioselective Synthesis of the Cyclohexene Subunit of (+)-Tetronolide

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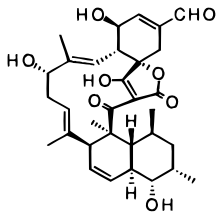
The development of methods allowing the diastereofacially selective construction of carbon−carbon bonds is one of the important thrusts of modern synthetic organic chemistry.[1] In our studies, several camphor-derived lactams have been found useful as auxiliaries for Diels−Alder, [2 + 2] cycloaddition, alkylation, and aldol condensation reactions.[2] Ongoing efforts directed toward the enantioselective construction of (+)-tetronolide (**1**),[3−6] the aglycon of the stereochemically complex natural antitumor tetrocarcins required methodology for the construction of enantiomerically pure hydroxy ester **2**. Prior studies from our laboratories have realized significant progress toward **1**, including the development of a sequence that afforded (±)-**2**.[7−9] We hoped to take advantage of the



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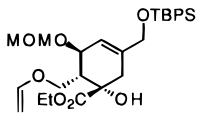

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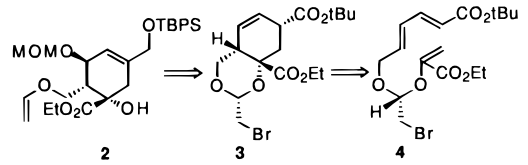
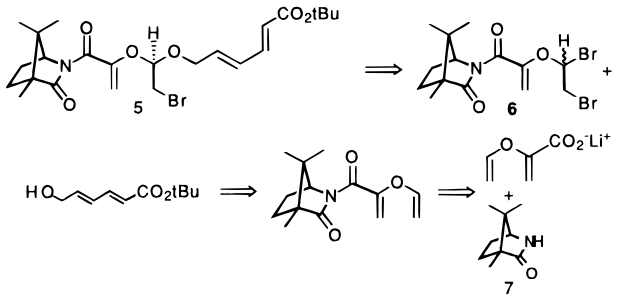
general strategy employed previously, in which (±)-**2** was derived via bicyclic acetal **3** from mixed acetal **4** by means of an *exo* selective intramolecular [4 + 2] cycloaddition (Scheme 1).[8] Thus, the problem was reduced to the enantioselective construction of mixed acetal **4**.

Since no suitable methodology existed, we developed the first such methodology based on a novel enantioselective synthesis of the key mixed acetal (*R*)-**4** using a chiral auxiliary-mediated substitution *via* neighboring group participation.[10]

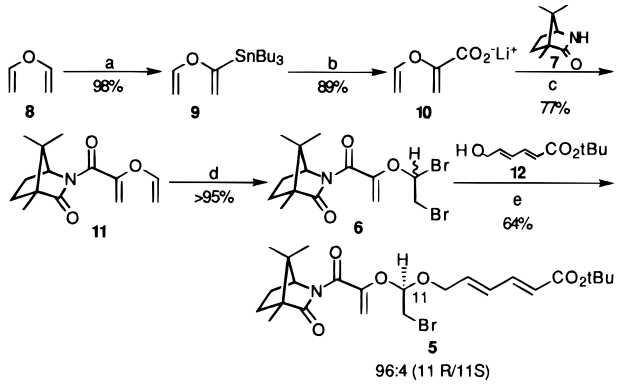
Scheme 1



Scheme 2



Scheme 3[a]



[a] Key: (a) *n*-BuLi (1.1 equiv), KO-t-Bu (1.1 equiv), THF, -78 °C, then *n*-Bu_3SnCl; (b) *n*-BuLi (1 equiv), THF, −78 °C then CO_2(g); (c) **10** (2 equiv), $PhSO_2Cl$ (1.5 equiv), TMEDA (4.8 equiv), THF, −78 °C, then lithio **7** [from **7** and *n*-BuLi (1 equiv)], THF, 0 °C; (d) Br_2 (1 equiv), Na_2CO_3, CH_2Cl_2, −78 °C; (e) AgOTf (1 equiv), **12** (1.3 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, slow addition of solution of **6** (1 equiv), −78 °C → rt.

Incorporation of bicyclic lactam (1*R*)-**7**,[2] into key dibromo ether precursor **6** should permit formation of diastereomerically pure mixed acetal **5** (Scheme 2). Participation of one of the imide carbonyl groups of the controller unit should rigidify the reacting array of atoms restricting the conformations available, and serve to differentiate the faces of the reacting center during the coupling.

As depicted in Scheme 3, preparation of dibromo ether **6** begins with divinyl ether (**8**). Metalation of **8** with *n*-BuLi and KO-*t*-Bu (Schlosser's base) followed by trapping with *n*-Bu_3SnCl affords the useful vinylstannane **9** in 98% yield.[11] Subsequent transmetalation of **9** with *n*-BuLi followed by carboxylation with CO_2(g) provided the lithium carboxylate salt **10** in 89% yield.[12] Exposure of **10** to $PhSO_2Cl$ in the presence of TMEDA generates the related symmetrical anhydride, which is condensed *in situ* with the lithium salt of **7** to afford the enol

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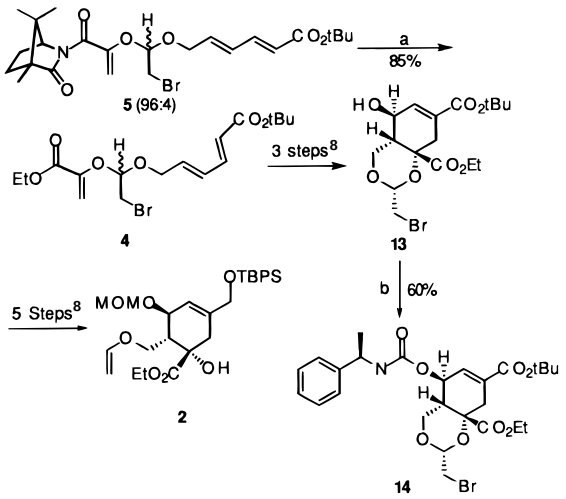
Scheme 4[a]

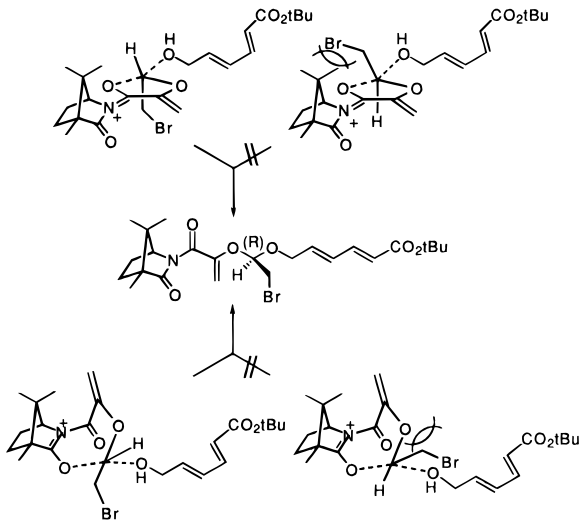


[a] Key: (a) $Ti(OEt)_4$, $PhCH_3$, rt, 4 h; (b) (*R*)-(+)-1-PhEtNCO, Et_3N, THF, Δ.

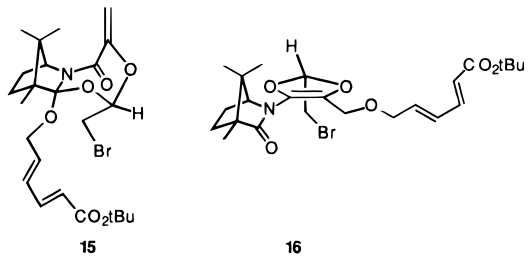
pyruvate imide **11** in 77% overall yield.[13] Regioselective addition of Br_2 to the more electrophilic vinyl ether affords the key, highly sensitive, dibromo ether **6** (5−6:1 ratio of diastereomers) in greater than 95% yield.[14] The neat oily dibromo ether **6** was found to be very sensitive to presumably acid catalyzed epimerization affording an ∼1:1 mixture of diastereomers on standing at ambient temperature.

Thus, for the crucial coupling, the CH_2Cl_2 solution of the crude dibromo ether **6** is immediately added slowly to a CH_2Cl_2 solution of AgOTf (1 equiv), dienol ester **12** (1.3 equiv),[8] and 2,6-lutidine (1.5 equiv) at −78 °C followed by gradual warming to room temperature. *Under these carefully defined conditions, the desired mixed bromo acetal* ***5*** *was obtained as a 96:4 mixture of diastereomers in 64% yield.* At this juncture, the configuration of the newly created asymmetric center at the mixed acetal carbon could not be readily discerned from spectroscopic data. Therefore, the mixture of bromo acetals **5** was transformed via triene ester **4** to the allylic alcohol **13** as depicted in Scheme 4. Unfortunately, mixed acetal imide **5** has, up to now, proven unsuitable for use in the Diels−Alder cycloaddition owing to its instability to a variety of Lewis acids. Consequently, **5** was smoothly converted to ester **4** in 92% yield upon treatment with $Ti(OEt)_4$ (3 equiv) in toluene at 25 °C with near-quantitative recovery of the lactam **7**. Using the sequence previously documented for the racemic series, enantiomerically enriched bromo acetal ester **4** was efficiently transformed to allylic alcohol **13** by [4 + 2] cycloaddition and epoxidation, followed by exposure to DBU.[8] Allylic alcohol **13** afforded, upon treament with (*R*)-(+)-α-methylbenzyl isocyanate, a crystalline carbamate **14** as a single detectable diastereomer (500 MHz ^1H NMR). Single-crystal X-ray analysis of **14** unambiguously determined the configuration at the acetal center in the major diastereomer of mixed bromo acetal **5** to be *R* as is required for conversion to (+)-**2**.[15] Alcohol **13** was then efficiently converted in five steps to enantiomerically pure (+)-**2** having $[\alpha]^{25}_D$ 34.4° (*c* 2.9, CH_2Cl_2) as previously described.[8]

Scheme 5



The magnitude of the diastereoselectivity observed in the condensation to afford triene (*R*)-**5**, as described, is particularly noteworthy considering the distal relationship of the controller unit with respect to the newly formed chiral center. This result certainly suggests an intimate participation of the controller unit within the transition state(s) possibly as proposed in Scheme 5. The transition state(s) lacking nonbonded interactions between the bromomethyl group and controller unit or side chain are favored with nucleophilic attack by the alcohol *anti* to the participating chiral auxiliary. Formation of the desired *R* isomer of **5** in an overall double inversion was obtained as is typically observed in cases of neighboring group participation.[10] This model is consistent with the absolute stereochemistry observed for **5** as confirmed by the results of X-ray analysis of carbamate **14** and is supported by the isolation of **15** and **16** as minor byproducts of the condensation.



Efforts to extend this novel approach to other useful complex acetals as well as synthetic studies directed toward the completion of the enantioselective total synthesis of tetronolide will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for compounds **3**−**6**, **9**−**11**, **13**, **14** and an Ortep drawing of the X-ray model for **14** (7 pages).

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(14) Owing to the sensitivity of the dibromide **6**, handling is minimized. The methylene chloride solution of **6** is filtered and partially concentrated prior to direct addition to the coupling reaction. Dibromide **6** was found to rapidly epimerize upon concentration to a neat liquid. Care is taken to avoid exposure of the solution of **6** to moisture as traces of HBr apparently catalyze rapid equilibration of **6**.

(15) The details of the single-crystal X-ray analysis of carbamate **14** will be published as part of a full account of these studies.