The First Synthesis of a Daphnane Diterpene: The Enantiocontrolled Total Synthesis of (+)-Resiniferatoxin

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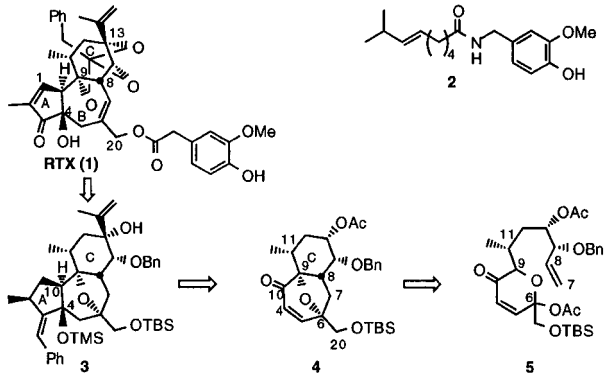
Resiniferatoxin (RTX, **1**) is a daphnane diterpene, identified in the latex of *Euphorbia resinifera* on the basis of its extraordinary irritant activity.[1] While structurally related to the potent tumor-promoting phorbol esters,[2] RTX is not a tumor promoter[3] and does not compete for the phorbol ester binding site on protein kinase C.[4] It does, however, exhibit activity in common with capsaicin (**2**), the major active constituent of red peppers.[5] In addition to its widely appreciated culinary use, capsaicin is the active ingredient in several commercial analgesic formulations and is also of interest as an antinociceptive agent and antifeedant.[6] Exhibiting potencies 10^3 to 10^5 times greater than capsaicin in many assays, RTX itself is of special therapeutic interest as an analgesic agent, particularly for the treatment of pain associated with diabetic polyneuropathy and postherpetic neuralgia.[7] In addition, RTX and its analogs serve as key probes for biochemical investigations of the relatively little studied vanilloid receptor.[8] Notwithstanding the remarkably long (>2000 years) continuous therapeutic use of daphnane extracts,[5a] the complexity and restricted availability of daphnanes and their analogs have greatly limited studies on their molecular mode of action.[9,10]

We describe herein the asymmetric synthesis of RTX (**1**), which marks the first synthesis of a daphnane, a family consisting of over 120 members.[11] Our synthesis was designed around the use of an uniquely complex oxidopyrylium cycloaddition (**5** → **4**) to set the daphnane BC-rings and relative stereochemistry at C8 and C9. The oxygen bridge of the cycloadduct was subsequently expected to protect the C9 hydroxyl group and to bias conformationally the otherwise flexible B-ring in order to control stereogenesis at C4 and C10 and attachment of the A-ring (**4** → **3**). Introduction of the ortho ester and the C20 homovanillyl chain was scheduled toward the end of the synthesis in order to minimize handling of active intermediates and to maximize flexibility with respect to analog preparation.

Scheme 1



Absolute stereochemistry was controlled in the first step of our synthesis (Scheme 2) through the known epoxidation[12] of **7** (51%, 98% enantiomeric excess (ee)[12b] which gave after protection (95%) epoxide **6**. Opening of this epoxide with LiCCOEt, followed by lactone formation, and methylation yielded two lactones (87:13), of which *trans*-lactone **8** was the major isolated diastereomer (66%, 3 steps).[13] Reaction of **8** with lithiated *tert*-butyldimethylsilyl (TBS)-protected furfuryl alcohol gave only the monoaddition product **9** (98%). Protection of the C13 alcohol as acetate **10** (97%), reduction of the ketone (~100%), and oxidation of the furan nucleus with *m*-chloroperoxybenzoic acid (*m*-CPBA) provided pyranone **11** (~100%) as an inconsequential mixture of stereoisomers. This mixture was then converted to the acetates **5** (96%) which underwent highly selective cycloaddition when heated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in acetonitrile to yield only the desired cycloadduct **4** (84%).[14]

Attachment of the A-ring to **4** requires that appendages be introduced at C4 and C10 in a *trans*-relationship. For this purpose, cycloadduct **4** was converted to enone **13** through a highly efficient five-step sequence (81% overall). Conjugate

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(14) The stereochemistry of cycloadduct **4** follows from its conversion to RTX and correlation with a derivative of an intermediate (compound **5** in ref 11c) in the synthesis of phorbol (see the Supporting Information).

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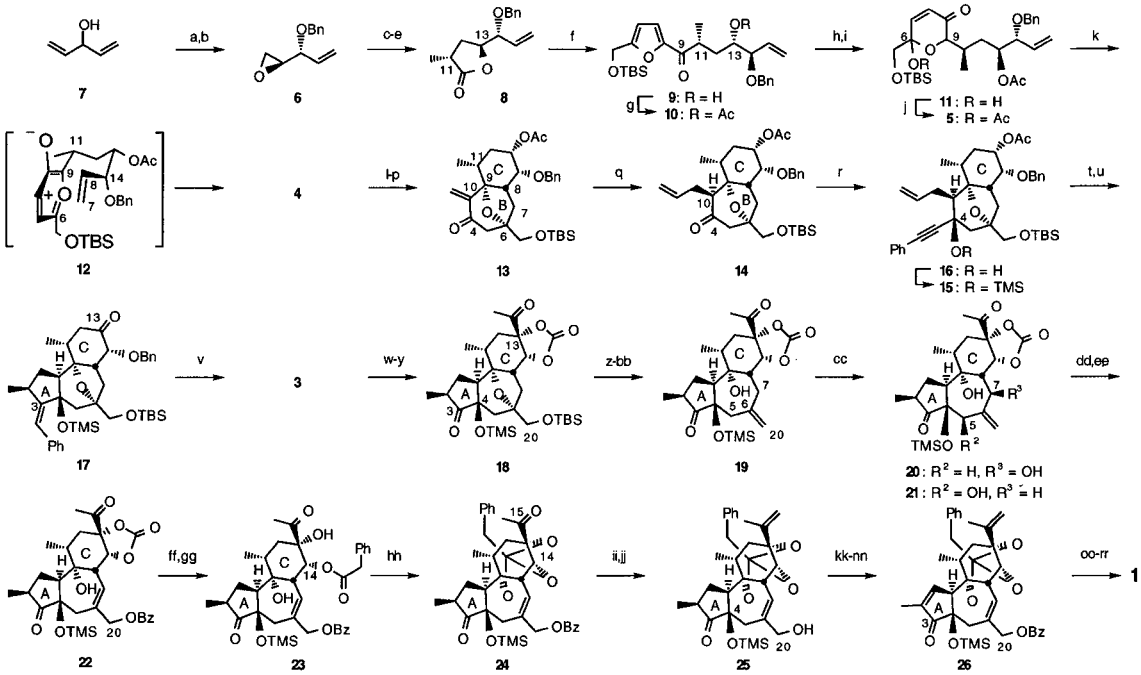
Scheme 2[a]



[a](a) Ti(O^{i}Pr)$_4$, (-) DIPT, *t*-BuO$_2$H, -15 °C, 51%. (b) BnBr, NaH, *n*-Bu$_4$NI, THF, 95%. (c) EtOCCLi, BF_3•OEt$_2$, THF, -78 °C. (d) TsOH, CH_2Cl_2, 81% (2 steps). (e) LDA, -78 °C, then MeI, see text. (f) TBS-protected furfuryl alcohol, *n*-BuLi, THF, -78 °C, then **8**, 98%. (g) AcCl, pyridine, CH_2Cl_2, 0 °C, 97%. (h) $NaBH_4$, MeOH, 0 °C, 100%. (i) *m*-CPBA, THF, 0 °C, 100%. (j) Ac_2O, DMAP, pyridine, 96%. (k) DBU, CH_3CN, 80 °C, 84%. (l) H_2 (49 psi), 10% Pd/C, EtOAc, 99%. (m) Ph_3PCH_2, THF, reflux, 97%. (n) AcCl, DMAP, pyridine, 0 °C, 98%. (o) SeO_2, *t*-BuO$_2$H, CH_2Cl_2, 93%. (p) MnO_2, CH_2Cl_2, 92%. (q) CH_2=CHLi, CuCN, Et_2O, -60 °C, 96%. (r) PhCCLi, LiBr, THF, -78 °C; MSTFA, **15** (43%) and **16** (33%). (s) TMSCl, imidazole, CH_2Cl_2, 80%. (t) Cp_2ZrBu_2, THF, -78 °C; HOAc, 90%. (u) TPAP, NMO, CH_2Cl_2, 94%. (v) CH_2=C(Me)MgBr, THF, 0 °C, 75%. (w) O_3, CH_2Cl_2-MeOH, -78 °C; $(NH_2)_2CS$, -78 °C, 65%. (x) H_2 (45 psi), 20% Pd(OH)$_2$/C, EtOAc, MeOH, 99%. (y) triphosgene, pyridine, CH_2Cl_2, 0 °C, 97%. (z) 49% HF, CH_3CN, 0 °C, 90%. (aa) Tf_2O, pyridine, CH_2Cl_2, 0 °C; *n*-Bu$_4$NI, CH_3CN, 96%. (bb) Rieke Zn, EtOH, reflux, 92%. (cc) SeO_2 (0.5 equiv)-*t*-BuO$_2$H, THF-HMPA (10:3), 80 °C, see text. (dd) $SOCl_2$, propylene oxide-Et_2O (1:2), 0 °C, 88%. (ee) AgOBz-KOBz, 18-crown-6, CH_3CN, 88%. (ff) 0.5 M NaOH in aq. dioxane, 73%. (gg) DMAP, 2,4,6-Cl_3-Ph-C(O)OC(O)CH_2Ph, toluene, 74%. (hh) 0.5% $HClO_4$ in MeOH, 46%. (ii) $TMSCH_2Li$, THF, -78 °C, 48%. (jj) 49% HF, CH_3CN, 86%. (kk) BzCl, pyridine, DMAP, CH_2Cl_2, 97%. (ll) MSTFA, DMAP, DABCO, CH_3CN, 110 °C, 98%. (mm) NBS, THF, 91%. (nn) Li_2CO_3, LiBr, DMF, 150 °C, 93%. (oo) TBAF, THF, 0 °C, 98%. (pp) Ba(OH)$_2$, MeOH, 98%. (qq) 2,4,6-Cl_3-PhC(O)OC(O)CH_2(4'-OAc)(3'-OMe)Ph, DMAP, toluene, 75%. (rr) pyrrolidine, CH_2Cl_2, 89%.

addition of vinyl cuprate to **13** followed by stereoelectronically controlled α-face protonation, dictated by the oxygen bridge, gave ketone **14** (96%). Addition of LiCCPh to the sterically less-encumbered face of **14**, followed by quenching of the resulting alkoxide with MSTFA,[15] afforded exclusively the *β*-substituted silyl ether **15** (43%) and alcohol **16** (33%). The latter can be converted to the former by independent silylation. Zirconocene-mediated cyclization[16] of **15**, one of the most complex examples of its kind, followed by oxidation of the resulting C13 hydroxy group with tetrapropylammonium perruthenate(VII) (TPAP) gave **17** in excellent yield (89%, 2 steps).

In a crucial test of stereocontrol, addition of isopropenylmagnesium bromide to **17** occurred as desired from the *β*-face of the C13 carbonyl to give a single adduct **3** (75%), possessing the complete daphnane framework. Ozonolysis of **3**, debenzylation of the product, and carbonate formation gave **18** (62%, 3 steps). Selective removal of the C20 TBS group with 49% aqueous HF (90%), conversion of the resulting alcohol to the iodide (96%), and iodo ether elimination[17] with activated zinc afforded **19** (92%). Allylic oxidation of **19** with SeO_2-*t*-BuO$_2$H in THF−HMPA (10:3) led to the formation of the desired C7 allylic alcohol **20** (61%) along with alcohol **21** (38%). Introduction of the C20 oxygen was accomplished by treatment of **20** with thionyl chloride followed by nucleophilic displacement by benzoate to give **22** (77%, 2 steps). Selective hydrolysis of the carbonate with 0.5 M NaOH furnished the corresponding diol (73%). Activation[18] of phenylacetic acid, followed by addtion to 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and the diol selectively provided the C14 ester **23** in 74% yield. Exposure of **23** to mildly acidic conditions[19] gave the ortho ester **24** in 46% yield.

The isopropenyl group was regenerated by a Peterson olefination of the C15 ketone to provide **25**.[20] Benzoylation of the C20 alcohol, C3 silyl enol ether formation, bromination, and elimination of HBr afforded the enone **26** in 80% overall yield.[11b] Finally, after the C4-TMS and C20 benzyl groups were cleaved (96%, 2 steps), the C20 alcohol was esterified with 4-acetoxy-3-methoxyphenyl acetic acid[19] and the acetate was removed to afford RTX (**1**, 66%, 2 steps).[21] Further synthetic, structure−activity, receptor characterization, and mode of action studies made possible through this effort are in progress.

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Supporting Information Available: Experimental procedures and characterization information (48 pages). See any current masthead page for ordering and Interenet access instructions.

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