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Tetrahedron: *Asymmetry* 14 (2003) 2883–2887

TETRAHEDRON: *ASYMMETRY*

A camphor-derived chiral auxiliary for hydroxyalkyl radicals

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Received 8 July 2003; accepted 28 July 2003

Abstract—A new camphor-derived chiral auxiliary for hydroxyalkyl radicals is described. The auxiliary is prepared by the Baeyer–Villiger oxidation of 3-fluorocamphor **12** to give lactone **14**, followed by its reduction to the lactol **16**. Compound **16** is converted to the acetal–ester **17** and then on to radical precursor **18**. A key feature of this auxiliary is the incorporation of a fluorine atom at C-3 (pyranoside numbering), which accelerates the Baeyer–Villiger reaction, results in complete anomeric control during auxiliary attachment, and stabilizes the resulting acetal center. The chiral radical derived from carboxylic acid **18** adds to methyl 2-trifluoroacetoxyacrylate to give adducts **22** and **23** with good diastereocontrol (ds from 3:1 at 0°C up to 4.5:1 at −78°C).

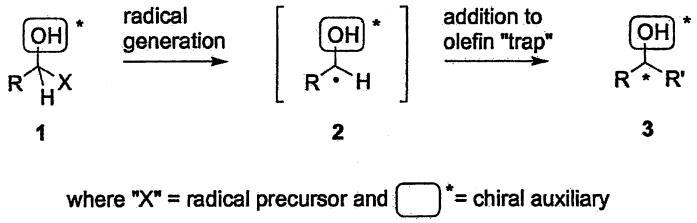
1. Introduction

We recently delineated our development of an effective pyranosidic chiral auxiliary for hydroxyalkyl radicals (Eq. (1)).[1] These studies began with a transition state model suggesting that alkenyl traps would prefer to approach the *Re*-face of the prochiral radical in order to avoid developing steric interference by H-6ax in the corresponding *Si*-TS (see **4** in Fig. 1).[2] Based on this model, the facial selectivity of this reaction should be enhanced by replacing H-6ax with an alkyl group as in **5a**. Unfortunately, the desired substitution would also be expected to initiate a conformational reorganization to **5b** as a consequence of the indicated 1,3-diaxial interaction making our hypothesis impossible to test. This led us to the conformationally-locked tetrahydropyran (THP) auxiliary in **6** and the 6,6-dimethyl-2-deoxyglucopyranosyl auxiliaries in **7** and *ent*-**8**. The key to all three of these auxiliaries was the incorporation of a fully substituted equatorial C-6 group to block the approach of the trap. While these systems did result in excellent levels of stereocontrol, the tBuTHP auxiliary required a rather lengthy asymmetric synthesis and was somewhat labile, while the sugar-derived auxiliaries possessed excess molecular baggage due to the extraneous protecting group functionality. We now report the synthesis and characterization of a new camphor-derived chiral auxiliary along with preliminary results regarding its influence on radical addition reactions.

2. Results and discussion

In our quest for a new pyranosidic chiral auxiliary that would be both easier and more economical to prepare, we turned to camphor as a chiral building block. The virtues associated with camphor-derived chiral auxiliaries have been reviewed.[3] Chief among these attributes are the commercial availability of both camphor antipodes and the ease of their chemical manipulation. One such auxiliary is embedded in the structure of radical **9**, analysis of which reveals that this system is essentially equivalent to the untestable modification **5a**. In this bicyclic auxiliary, the ethyl bridge precludes pyranoside ring-flipping to the alternative chair conformation while the 8-*endo*-methyl group destabilizes the boat conformation.

This auxiliary was prepared from the known Baeyer–Villiger product of D-camphor **10**. Unfortunately, a series of problems soon became apparent preventing successful implementation of this auxiliary. First, the



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doi:10.1016/j.tetasy.2003.07.014

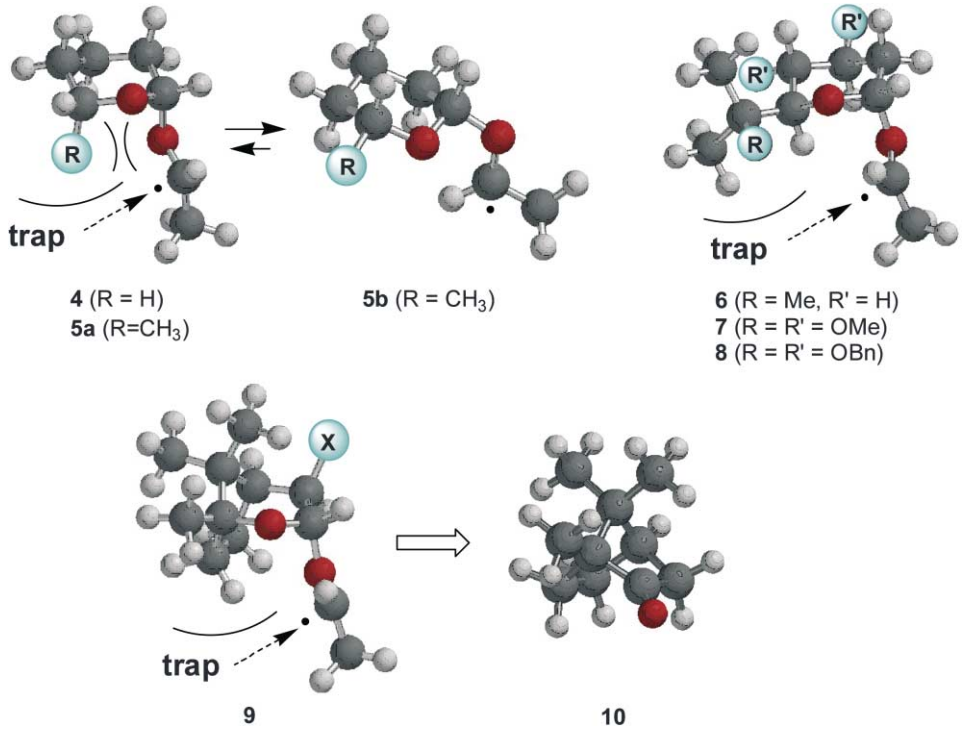
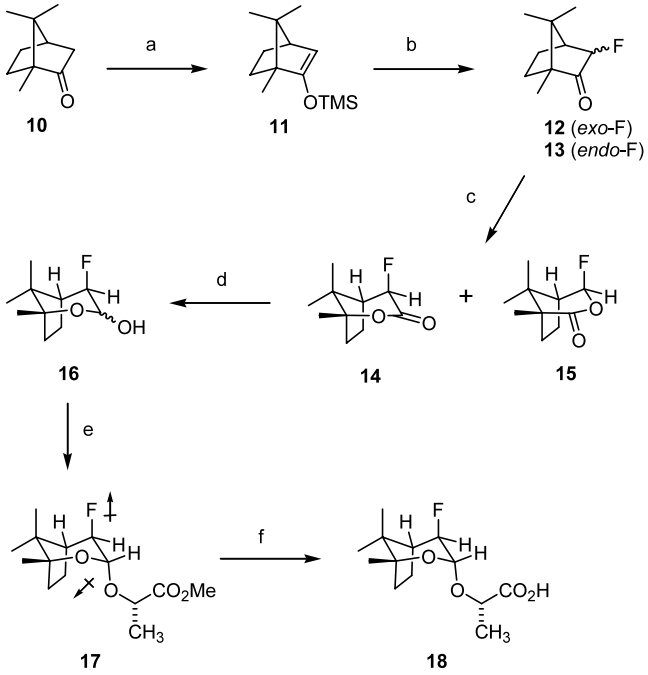


Figure 1. Three-dimensional representations of pyranosidic chiral auxiliaries for hydroxyalkyl radicals.[2]

Baeyer–Villiger reaction of camphor is inefficient and results in the production of both lactone regioisomers.[4,5] Second, formation of the mixed acetal from the condensation the corresponding lactol and methyl lactate actually favored formation of the undesired *exo*-diastereomer. Third, the acetal moiety itself is quite sensitive towards acid-catalyzed hydrolysis. This last problem was particularly vexing in the context of product purification and analysis of the radical addition diastereoselectivity. In fact, we found it impossible to isolate any radical addition products from reactions involving **9** (X = H).

Recalling a tactic that had been used to enhance the stability of thromboxane A analogs,[6] we turned to the incorporation of an electronegative fluorine atom at C-3 of **9** (X = F). Such a substitution was expected to both stabilize the acetal structure and destabilize the oxocarbenium intermediate that forms during acid-catalyzed decomposition. Additionally, the fluorine atom was also expected to accelerate the Baeyer–Villiger reaction and favorably influence the anomeric ratio.

The fluorinated chiral auxiliary was prepared and attached to our prototype radical precursor as shown in Scheme 1. The sequence began with the conversion of D-camphor **10** to its TMS enol ether **11** by the action of TMSOTf and base. The enol ether was not isolated but treated directly with 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™)[7] leading to a 2:1 mixture of the *exo*- and *endo*-fluorides **12** and **13** in 69% combined yield (over-



Scheme 1. *Reagents and conditions*: (a) TMSOTf (2.1 equiv.), Et_3N (2.4 equiv.), toluene, reflux; (b) F-TEDA-BF_4 (1.0 equiv.), DMF, 69% combined yield based on recovered **10**, **12**/**13** = 2:1; (c) mCPBA (1.7 equiv.), $NaHCO_3$ (1.7 equiv.), DCM, **14**: 36% yield, **15**: 30% yield; (d) DIBAL (1.4 equiv.), toluene, −78°C, quantitative; (e) (*S*)-methyl lactate (20 equiv.), cat. PPTS, toluene, reflux, 56% yield; (f) 1N NaOH, THF, quantitative.

Table 1. Radical additions to methyl 2-trifluoroacetoxyacrylate

Entry	Procedure[a]	Radical addition temperature (°C)	Diastereoselectivity **22**/**23**
1	A	−78	4.5:1
2	A	0	3:1
3	B	−78	4:1

[a] Procedure A utilized DCC for Barton esterification whereas procedure B utilized HOTT (see Section 3 for details).

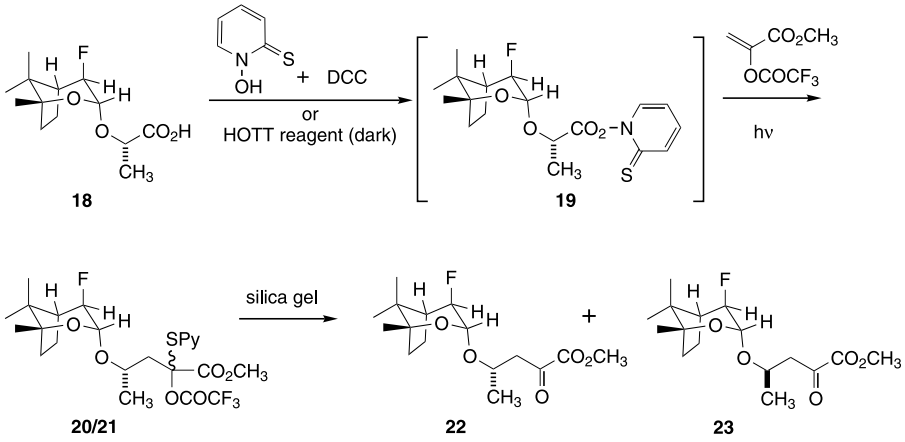
all from **10**). This reaction outcome differed from that of Rozen and Menahem, who obtained only the *endo*-isomer **13** when they reacted the corresponding enol acetate with the electrophilic mixture made from $CF_3CO_2Na+F_2$.[8] Separation of these isomeric fluorides by chromatography was very difficult. Fortunately, this was not necessary because the Baeyer–Villiger reaction of **12** proceeded at a much faster rate than **13** (resulting in an easier separation). Exposure of the mixture of **12** and **13** to buffered mCPBA proceeded smoothly to give 36% of the desired lactone **14** along with an equal amount of regioisomer **15** as well as unreacted **13** (24%). The increased proportion of undesired lactone in this reaction may be due to a stereoelectronic effect of the C–F bond.[9] Partial reduction of lactone **14** with DIBAL gave a mixture of lactols **16** in quantitative yield. This mixture was not separated but condensed directly with (*S*)-methyl lactate to give a single anomer **17** in 56% yield. The α-configuration of **17** was readily established by a $^3J_{HF}$ value of 19 Hz for coupling of the equatorial anomeric proton to the axial vicinal fluorine atom.[10] We tentatively ascribe this α-selectivity to an augmentation of the anomeric effect by the dipole moment associated with the axial C–F bond (see arrows in structure **17**). Saponification of **17** produced the corresponding carboxylic acid **18** in quantitative yield.

We next examined the addition of the radical **9** to methyl 2-trifluoroacetoxyacrylate[11] following our established protocol (Eq. (2)). The results of our preliminary studies are presented in Table 1. The diastereoselectivities of these reactions were determined by NMR from the ratio of α-ketoester adducts **22** and **23**. Our structural assignments are based upon NMR similarities to analogous α-ketoesters that we had characterized by chemical correlation. Even though the isolated yields of these products were not optimized, the diastereomeric ratios obtained in this manner and our conclusions are considered to be valid. Artificial enrichment was precluded by the fact that these adducts have identical chromatographic mobilities under the conditions used to purify the crude reaction mixtures. The observed diastereomer ratios suggest that the facial preference associated with this auxiliary is better than that of our original 2-deoxyglucopyranosidic auxiliary but not as good as their 6,6-dimethylated progeny. A possible explanation for this outcome may be gleaned from analysis of the radical **9** modeled in Figure 1. It is clear that the axially disposed CH_2 group at C-6 (pyranoside numbering) forces the axial substituent at C-1 to splay, resulting in a dihedral angle between O-1 and C-4 of −24° (instead of the ideal value of −60°). This conformational deviation makes attack of the radical *Si*-face more likely because the altered trap trajectory is less likely to encounter steric compression by the CH_2 group. Our analysis also suggests that reduction of anomeric splay will restore the high selectivities observed with our tBuTHP auxiliary. We are currently testing this hypothesis.

3. Experimental

3.1. General

Melting points were determined using a Mel-Temp Capillary melting point apparatus. All moisture-sensitive reactions were performed in an inert, dry atmosphere of argon. Reagent grade solvents were used for either chromatography or extraction. The following solvents and reagents were purified beyond commercial reagent grade. THF was distilled under argon from a purple solution of sodium–benzophenone ketyl. Toluene and DCM were distilled over CaH_2 under argon. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F-254 plates. The



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plates were visualized first with UV illumination followed by charring with 'Verghn's reagent' (12.5 g of ammonium molybdate and 0.5 g of ceric sulfate dissolved in 250 mL of 10% aq. H_2SO_4). Flash column chromatography was performed using silica gel (230–400 mesh). The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis.

3.2. Synthesis of 3-fluoro-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-ones 12 and 13

A solution of D-camphor (340 mg, 2.23 mmol) in toluene (5 mL) under argon was treated with triethylamine (0.75 mL, 5.4 mmol) and TMSOTf (0.83 mL, 4.6 mmol) and refluxed for 1.5 h. The solution was cooled to rt, diluted with 100 mL of hexanes, washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The residue was suspended in DMF (30 mL) and treated with F-TEDA-BF_4 (789 mg, 2.23 mmol) at rt under argon. After 15 min, the solution was reacted with 2.3 mL (2.3 mmol) of 1.0 M $Bu_4N^+F^-$ in THF for 5 min and then poured slowly into 100 mL of H_2O with stirring. The resulting solution was stirred for 1 h and extracted with hexanes. The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography (1:1 DCM–pentane) to afford 69% of an inseparable 2:1 mixture of **12** and **13**[8] as a white solid along with recovered camphor **10**. The mixture of **12** and **13** was used directly in the next step. R_f 0.62 (1:1 DCM–pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H, *endo*), 0.91 (s, 3H, *exo*), 0.93 (s, 6H, *exo*), 0.95 (s, 3H, *endo*), 1.02 (s, 3H, *endo*), 1.25–1.88 (m, 7H, both), 1.95–2.04 (m, 1H, *exo*), 2.23 (dd, $J=5.2$, 11.5 Hz, 1H, *exo*), 2.40 (t, $J=6.5$ Hz, 1H, *endo*), 4.37 (d, $J=53.2$ Hz, 1H, *exo*), 4.89 (dd, $J=5.1$, 52.5 Hz, 1H, *endo*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1 (both), 93.2 (d, $J=$ 198.4 Hz, *exo*), 92.1 (d, $J=193.7$ Hz, *endo*), 57.2 (both), 48.3 (d, $J=15.5$ Hz, *exo*), 47.6 (d, $J=14.3$ Hz, *endo*), 31.9 (both), 28.5 (*exo*), 23.2 (*exo*), 20.8 (*exo*), 20.0 (*endo*), 19.5 (*exo*), 18.6 (*endo*), 18.0 (*endo*), 17.8 (*endo*), 9.3 (both).

3.3. 4-Fluoro-1,8,8-trimethyl-2-oxa-bicyclo[3.2.1]octan-3-one 14

To a solution of *exo*/*endo* mixture **12** and **13** (2:1 ratio) (500 mg, 2.94 mmol) in DCM (7 mL) was added mCPBA (857 mg, 4.97 mmol) and $NaHCO_3$ (418 mg, 4.98 mmol) at rt. The reaction mixture was stirred for 1.5 h, diluted with saturated $NaHCO_3$ and DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography (1:1 DCM–pentane) to afford 36% of **14**, 30% of **15** and 24% of **13**. For **14**: R_f 0.21(1:1 DCM–pentane); white solid; mp 78–79°C (recrystallized from hexanes–Et_2O); $[\alpha]_D^{20}=-26$ (*c* 1.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.09 (d, $J=3.7$ Hz, 3H), 1.33 (s, 3H), 1.94–2.27 (m, 4H), 2.37 (dd, $J=1.4$, 7.5 Hz, 1H), 4.63 (dd, $J=1.4$, 46.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.6, 94.9, 90.6 (d, $J=186.1$ Hz), 48.1 (d, $J=17.4$ Hz), 43.1, 35.5, 23.9, 22.6, 18.3, 17.8; EIMS (*m*/*z*) MH^+ calcd for $C_{10}H_{15}FO_2$ 187.1134; found 187.1128. For **15**: R_f 0.42 (1:1 DCM–pentane); white solid; mp 145–146°C (recrystallized from hexanes–Et_2O); $[\alpha]_D^{20}=+35$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.19 (s, 3H), 1.20 (s, 3H), 1.56–1.67 (m, 1H), 1.80–2.22 (m, 4H), 5.71 (dd, $J=1.1$, 58.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.2, 111.4 (d, $J=229.7$ Hz), 53.6, 47.6 (d, $J=17.1$ Hz), 43.1, 33.8, 22.9, 22.8, 20.8, 14.1; EIMS (*m*/*z*) M^+ calcd for $C_{10}H_{15}FO_2$ 186.1056; found 186.1067.

3.4. 4-Fluoro-1,8,8-trimethyl-2-oxa-bicyclo[3.2.1]octan-3-ols 16

To a solution of lactone **14** (96 mg, 0.52 mmol) in toluene (3 mL) at −78°C was added DIBAL (1.5 M in toluene, 0.46 mL, 0.69 mmol). After 30 min the reaction mixture was quenched with acetone, warmed to rt, diluted with aqueous potassium sodium tartrate, stirred for 1 h and diluted with EtOAc, water and brine. The aqueous phase was extracted with Et_2O (2×), and the combined organic extracts were washed with brine (1×), dried over $MgSO_4$ and concentrated to afford the diastereomeric mixture of lactols **16**; R_f 0.55 (1:1 hexanes–EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.86 (s, 3H), 1.12 (s, 3H), 1.13 (s, 6H), 1.15 (s, 3H), 1.63–2.28 (m, 10H), 4.38 (ddd, $J=2.6$, 4.2, 50.9 Hz, 1H, major), 4.47 (dd, $J=3.1$, 48.9 Hz, 1H, minor), 4.96 (dd, $J=2.6$, 19.6 Hz, 1H, major), 5.23 (dd, $J=1.1$, 18.8 Hz, 1H, minor); ^{13}C NMR (50 MHz, $CDCl_3$) δ 95.0 (d, $J=177.0$ Hz, minor), 94.4 (d, $J=37.1$ Hz, minor), 92.4 (d, $J=187.1$ Hz, major), 89.6 (d, $J=16.5$ Hz, major), 85.4 (major), 85.3 (minor), 47.8 (minor), 47.5 (major), 42.9 (major), 41.5 (minor), 34.5 (minor), 32.4 (major), 24.9 (minor), 24.4 (major), 22.1 (d, $J=4.4$ Hz, major), 21.5 (d, $J=12.8$ Hz, minor), 19.2 (major), 19.1 (minor), 19.0 (minor), 18.7 (major); EIMS (*m*/*z*) M^+ calcd for $C_{10}H_{17}FO_2$ 188.1213; found 188.1215.

3.5. 2-(4-Fluoro-1,8,8-trimethyl-2-oxa-bicyclo[3.2.1]oct-3-yloxy)-propionic acid methyl ester 17

To a solution of lactols **16** (57 mg, 0.30 mmol) in toluene (3 mL) was added (*S*)-methyl lactate (0.6 mL, 6 mmol) and a catalytic amount of PPTS (3 mg, 0.01 mmol). The reaction mixture was heated to reflux for 1 h under argon, then cooled to rt and washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, concentrated and purified by flash column chromatography (5:1 hexanes–EtOAc) to afford only α-anomer **17** as a colorless liquid, 56% yield, R_f 0.56 (3:1 hexanes–EtOAc); $[\alpha]_D^{20}=-128$ (*c* 2.10, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.06 (d, $J=4.8$ Hz, 3H), 1.11 (s, 3H), 1.41 (d, $J=6.9$ Hz, 3H), 1.56–1.67 (m, 1H), 1.72–1.98 (m, 3H), 2.09–2.18 (m, 1H), 3.72 (s, 3H), 4.51 (q, $J=6.9$ Hz, 1H), 4.54 (dd, $J=3.3$, 48.7 Hz, 1H), 4.91 (dd, $J=1.1$, 18.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.4, 97.8 (d, $J=37.0$ Hz), 94.7 (d, $J=177.8$ Hz), 85.1, 69.5, 51.9, 47.4 (d, $J=16.9$ Hz), 41.9, 34.1, 24.9, 21.2 (d, $J=12.8$ Hz), 19.0, 18.7; EIMS (*m*/*z*) M^+ calcd for $C_{14}H_{23}FO_4$ 274.1580; found 274.1567.

3.6. 2-(4-Fluoro-1,8,8-trimethyl-2-oxa-bicyclo[3.2.1]oct-3-yloxy)-propionic acid 18

A solution of the lactate ester **17** (38 mg, 0.14 mmol) in THF (1 mL) and 1N NaOH (1 mL) was stirred at rt for 1 h. The reaction was quenched with pH 4 buffer (1 mL), the layers were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to afford **18** as colorless liquid; R_f 0.11 (2:1 hexanes–EtOAc); $[\alpha]_D^{20} = -146$ (*c* 0.42, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.00 (d, $J = 4.8$ Hz, 3H), 1.06 (s, 3H), 1.40 (d, $J = 7.0$ Hz, 3H), 1.53 (dd, $J = 3.3$, 12.8 Hz, 1H), 1.66–2.06 (m, 4H), 4.47 (q, $J = 7.0$ Hz, 1H), 4.48 (dd, $J = 3.3$, 48.6 Hz, 1H), 4.91 (dd, $J = 0.9$, 18.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.7, 97.9 (d, $J = 37.3$ Hz), 94.6 (d, $J = 178.1$ Hz), 85.4, 69.4, 47.5 (d, $J = 16.9$ Hz), 41.9, 34.1, 29.7, 24.9, 21.4, 19.1, 18.6; EIMS (*m*/*z*) M^+ calcd for $C_{13}H_{21}FO_4$ 260.1424; found 260.1433.

3.7. 4-(4-Fluoro-1,8,8-trimethyl-2-oxa-bicyclo[3.2.1]oct-3-yloxy)-2-oxopentanoic acid methyl esters 22 and 23

Procedure A; To a 0.1 M solution of carboxylic acid **18** and 2-mercaptopyridine-*N*-oxide (1.5 equiv.) in freshly distilled DCM in an aluminum foil-covered flask was added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 1.5 equiv.) under argon. The reaction was stirred at rt in the dark for 1 h (judged to be complete by IR), cooled to −78 or to 0°C, methyl 2-trifluoroacetoxyacrylate (5 equiv.) was added, and the mixture was irradiated using a 300 W sunlamp until the Barton ester had been consumed as evidenced by TLC. The reaction mixture was filtered through silica gel washing with Et_2O, concentrated and subjected to flash column chromatography (6:1 hexanes–EtOAc) to afford the pure inseparable diastereomers in 13–20% yields.

Procedure B; A dry THF solution of the carboxylic acid **18** was added to an aluminum foil-covered flask containing a dry CH_3CN solution of (*S*)-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyl-thiouronium hexafluorophosphate HOTT (1.5 equiv.) and DMAP (0.1 equiv.) at rt under argon. The final concentration of acid was 0.1 M in (3:1) THF–CH_3CN. Diisopropylethylamine (DIPEA) (3 equiv.) was added to the mixture and the resulting solution was stirred in the dark for 1 h (judged to be complete by IR) and then processed as in procedure A affording a 14–23% yield of **22** and **23**. The results of these experiments are presented in Table 1.

For **22** and **23**; R_f 0.31 (4:1 hexanes–EtOAc); ^1H NMR (600 MHz, $CDCl_3$) δ 0.85 (s, 6H, both), 1.06 (d, $J = 4.8$ Hz, 3H, major), 1.09 (s, 3H, minor), 1.11 (s, 6H, both), 1.23 (d, $J = 6.4$ Hz, 3H, minor), 1.33 (d, $J = 6.3$ Hz, 3H, major), 1.36–1.48 (m, 1H), 1.69–1.85 (m, 6H, both), 2.05–2.14 (m, 3H, both), 2.89 (dd, $J = 5.5$, 16.1 Hz, 1H, minor), 2.90 (dd, $J = 5.6$, 16.4 Hz, 1H, major), 3.04 (dd, $J = 6.8$, 16.4 Hz, major), 3.18 (dd, $J = 7.0$, 16.1 Hz, 1H, minor), 3.87 (s, 6H, both), 4.29–4.33 (m, 2H, both), 4.31 (dd, $J = 3.2$, 48.9 Hz, 1H, major), 4.33 (dd, $J = 3.1$, 48.8 Hz, 1H, minor), 4.92 (d, $J = 19.4$ Hz, 1H, major), 4.93 (d, $J = 19.9$ Hz, 1H, minor);^{13}C NMR (50 MHz, $CDCl_3$) δ 192.5 (major), 192.1 (minor), 161.5 (major), 161.3 (minor), 99.2 (d, $J = 36.8$ Hz, major), 96.3 (d, $J = 37.1$ Hz, minor), 95.8 (d, $J = 177.8$ Hz, minor), 95.3 (d, $J = 178.1$ Hz, major), 84.9 (both), 70.8 (major), 67.9 (minor), 53.0 (both), 47.6 (d, $J = 16.8$ Hz, minor), 47.5 (d, $J = 16.8$ Hz, major), 46.6 (minor), 45.8 (minor), 41.8 (both), 33.7 (both), 24.8 (both), 21.8 (both), 21.3 (d, $J = 13.0$ Hz, minor), 21.2 (d, $J = 12.9$ Hz, major), 19.2 (major), 19.0 (major), 18.9 (minor), 18.7 (minor); EIMS (*m*/*z*) M^+ calcd for $C_{16}H_{25}FO_5$ 316.1686; found 316.1675.

Acknowledgements

This work was supported by the National Science Foundation under Grant CHE-0111831. We wish to thank Scott Medical/Air Products for providing us with a generous sample of F-TMEDA-BF_4 (Selectfluor™).

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