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Synthesis of Chiral Ligands from Hydrindene Diols with a Consecutive Heterodomino Transformation as the Key Reaction Step

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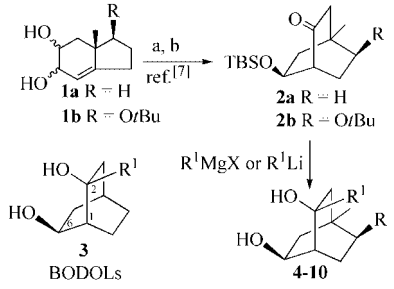
We report here the elaboration of a bicyclo[2.2.2]octane system, synthesized by a consecutive domino process, towards highly functionalized stereopure derivatives, which could be used as multidentate ligands for the generation of asymmetric catalysts.

Introduction

Ever since the introduction by Kagan of the C_2-symmetric ligand DIOP in 1971,[1] a plethora of chiral ligands were prepared and tested and they demonstrated the beneficial effects of the C_2 symmetry compared with nonsymmetrical ligands. Even though the greater part of chiral ligands[2] possess C_2 symmetry, efficient nonsymmetrical ligands that allow for high enantiocontrol are also known in the literature: a desymmetrized DIOP ligand gave higher optical (and chemical) yields.[3] Waldmann et al. introduced the C_2-symmetric bicyclo[2.2.2]octane framework as a TADDOL analogue (1,4-diols).[4] More recently, Frejd et al.[5] introduced a new class of 1,3-diols that are based upon 2-substituted bicyclo[2.2.2]octane-2,6-diols (BODOLs, **3**, Scheme 1). These bicyclic 1,3-diols were prepared by baker's yeast monoreduction of bicyclo[2.2.2]octane-2,6-dione, followed by protection of the alcohol, introduction of a sidearm in the 2-position by nucleophilic addition to the carbonyl group, and subsequent deprotection. A number of chiral bidentate ligands were synthesized and evaluated as ligands for asymmetric catalysis by this research team.

There are several routes in the literature for the preparation of bicyclo[2.2.2]octane derivatives.[6] For the current methodology to be useful in chiral ligand preparation, straightforward methods for the synthesis of the requisite bicyclic framework are important. A new class of domino transformations has been developed in our laboratories through the reaction of hydrindene diols of type **1** with two oxidants and one base in a consecutive way.[7] An advantage of this method, the combination of two heterodomino reactions[8] (ring expansion/ring system interchange), lies in that the whole transformation can be carried out in a one-pot operation. The purpose of this work is to put forward concise routes, which would allow for the stereoclean construction of optically pure hydroxylated bicyclic frameworks starting from easily available type **1** hydrindene diols[9] as portrayed in Scheme 1. To this aim, it was sought to exploit the rigid, stereochemically well-defined bicyclo[2.2.2]octane skeleton of **2** with appropriate substituents that could first serve as control elements and subsequently as chelating arms for several metals.



Scheme 1. a) 1.2 equiv. $PhI(OAc)_2$, 24 h, then 1.2 equiv. $Pb(OAc)_4$, PhMe, 15 h; then K_2CO_3/MeOH, H_2O, 25 °C. b) TBSCl, DMF-Imidazole, 0 °C, 1 h 30 min.

Results and Discussion

Elaboration of Bidentate Ligands

Our parent target system was thus **2**, prepared in two steps from hydrindene diols of type **1** as shown in Scheme 1.

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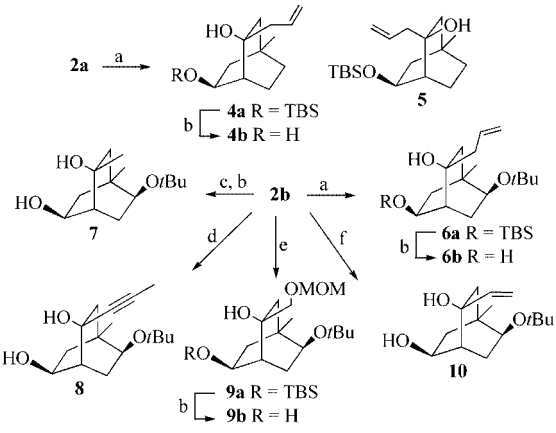
Insofar as C-2 carbinol stereoselectivity is concerned, it was likely that increased selectivity could be acquired by increasing the steric hindrance in the carbonyl substrate, as exemplified by 1,3-control of the bulky TBS group in **2a** and **2b**. The synthesis of bidentate ligands involves direct nucleophilic addition at the carbonyl (Scheme 2), whereas for the synthesis of tridentate ligands we favored acyloin formation by ozonolysis of silyl enol ether **11** (Scheme 3) followed by nucleophilic addition (Scheme 4).

The very promising results obtained by Frejd et al. with BODOLs of type **3** (Scheme 1) encouraged us to begin with **2a**. Thus, our first target was bidentate ligand **4b**, and addition of commercially available allylmagnesium bromide seemed to be an efficient route. Upon subjection of **2a** to standard Grignard addition conditions (AllylMgBr, THF, –78 °C, 30 min), a mixture of adducts **4a** (50%) and **5** (12%) was obtained along with **4b** (36%) where the TBS protecting group was cleaved. Even though the isolated chemical yield was excellent, the selectivity for the desired isomer was poor; unwanted **5** was present in 12%.[10]

We thus switched to **2b**, where the TBS protecting group was used as a steric director, in combination with the O*t*Bu substituent, in a stereodefined construction of both bi- and tridentate ligands. Contrary to sterically unbiased **2a**, and much to our pleasure, our parent target systems **2b** for bidentate and **12b** for tridentate ligands (Schemes 2 and 4, respectively) underwent nucleophilic additions with complete selectivity in the required direction and showed a complete *syn* preference with respect to the O*t*Bu substituent. Initial efforts were devoted to optimize the yield of carbinols **6**–**10** (either in its TBS-protected form or as a diol).

A four- to fivefold excess of the nucleophile was found to give good results. Additional reaction parameters such as temperature and time as well as choice of the quenching agent were also looked at (optimal conditions are described in detail in the Experimental Section).

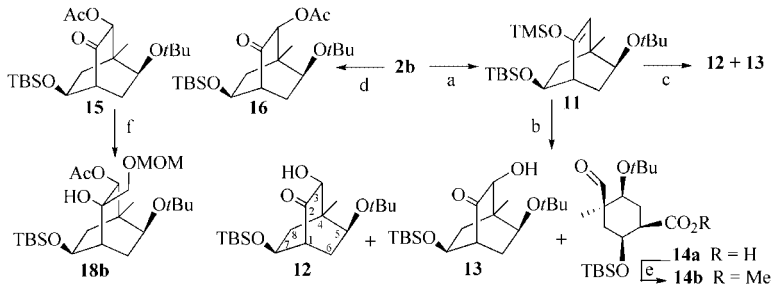
Preparation of bicyclo[2.2.2]octane derived 1,3-bidentates was straightforward. Starting from **2b**, nucleophilic addition (Grignard or RLi, THF, –78 °C) and subsequent fluoride deprotection (nBu$_4$NF, THF, 60 °C) afforded the targets in high chemical yields and complete selectivity. Upon prolonged reaction times, removal of the TBS group was observed; in some cases, such as **8**, the fluoride deprotection step was unnecessary. By means of these operationally simple reactions, enantiomerically pure bicyclic 1,3-diols **6**–**10**, potential bidentate ligands, were readily available in multigram scale; their synthesis is portrayed in Scheme 2. When bicyclic aldol **2b** was treated with excess allylmagnesium bromide (1 M in Et$_2$O, 5 equiv.) at –78 °C for 1 h, TBS-protected carbinol **6a** was furnished in 45% isolated yield along with 35% yield of target bidentate ligand **6b**. When the reaction was left overnight at room temperature, a 56% yield of **6b** was obtained along with 22% yield of **6a**. Fluoride deprotection (TBAF, THF)[11] then removed the silyl group, which resisted direct deprotection in the reaction medium to afford bidentate ligand **6b** in 90% yield. Exposure of **2b** to an excess of MeLi (1.6 M in Et$_2$O, 7 equiv.), in dry THF cooled to –78 °C, followed by fluoride deprotection (TBAF, 1 h, 60 °C) afforded a 64% isolated yield of **7**. Reaction of **2b** with propynyllithium (prepared in situ from propyne, nBuLi, HMPA), in dry THF at –78 °C to 25 °C, for 1 h directly afforded desired diol **8** (70%); no TBS-protected diol was isolated under these conditions. Addition of α-alkoxyorganolithium, derived from Bu$_3$SnCH$_2$OMOM[12] by transmetalation with nBuL*i* (nBuLi, Bu$_3$SnCH$_2$OMOM, in dry THF, –78 °C, 20 min),[13] to **2b** gave a mixture of two products: **9a** and recovered starting material **2b** (87% in 1.9:1 ratio), which were separated by SiO$_2$ flash chromatography and isolated in their pure forms. Fluoride deprotection as above gave desired bidentate ligand **9b** in 78% combined yield. Finally, vinylmagnesium bromide (1 M in dry THF, –78 °C for 1 h, then overnight at 25 °C) addition to **2b** afforded bidentate ligand **10** in 73% isolated yield.



Scheme 2. a) AllylMgBr, Et$_2$O, –78 °C. b) TBAF, THF, 60 °C. c) MeLi, THF, –78 °C. d) Propyne, nBuLi, HMPA, –78 °C, to 25 °C. e) Bu$_3$SnCH$_2$OMOM, nBuLi, –78 °C. f) VinylMgBr, THF, –78 °C.

Elaboration of Tridentate Ligands

Because there is potential for novel tridentate ligands,[14] routes to conformationally restricted triols may be of interest. The three functional groups (free hydroxy, *t*Bu-protected hydroxy, and carbonyl) on each ring, combined with the efficient steric control ensured by the rigid bicyclic framework of **2b**, offer easy chemodifferentiation for further selective transformations. Inspired by the work published on BODOLs,[5] we decided to synthesize more oxygenated derivatives starting from **2b**, targeting 1,3,4-triols, which could be derived from **12** (Scheme 3). For the synthesis of the targeted tridentate ligands we needed to determine the stereochemistry of the added hydroxy group at C-3 and to obtain a high as possible ratio of **12**/**13** (or **15**/**16**) and therefore alternative methods of α-hydroxylation of **2b** were investigated. Direct acetoxylation of **2b** by treatment with Pb(OAc)$_4$ in benzene (90 °C, 2 d) afforded a modest 35% isolated yield of **15** along with 0.5% of **16** and unreacted starting material (40%). While the diastereoselectivity of the key hydroxylation reaction to provide **15**, a precursor to desired acyloin **12**, was excellent (70:1 in favor of **15**), the yield remained poor; therefore, an alternative method



Scheme 3. a) TMSOTf, collidine, CH_2Cl_2, 0 °C. b) O_3, MeOH, –78 °C, then HCl, THF, 25 °C. c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C. d) $Pb(OAc)_4$, PhH, 90 °C. e) $TMSCHN_2$, Et_2O, MeOH, 0 °C. f) Bu_3SnCH_2OMOM, *n*BuLi, –78 °C.

of α-hydroxylation was investigated. Attempted next, the α-hydroxylation of **2b** by the oxidation of its corresponding silyl enol ether with a peracid proved less effective (Rubottom hydroxylation).[15] Thus, generation of silyl enol ether **11** by sequential treatment of **2b** with TMSOTf in the presence of collidine, in CH_2Cl_2 at 0 °C, followed by the addition of *m*-CPBA and $NaHCO_3$ in dry CH_2Cl_2 at 0 °C for 20 min gave desired α-acetoxy ketone **12** in only 29% isolated yield, together with 39% of **13** and 25% of recovered starting material, as portrayed in Scheme 3. Replacement of the oxidant by MTO–H_2O_2[16] failed to give the desired acyloin and the starting material was recovered intact. In a better approach, **2b** was transformed by a three step sequence (TMSOTf, collidine, CH_2Cl_2, 0 °C, 2 h, followed by ozonolysis in CH_2Cl_2 at –78 °C, and subsequent desilylation with HCl in THF, at 25 °C for 20 min) to monoprotected α-ketol **12** in 58% yield, along with epimer **13** (12%), and the normal ozonolysis product **14a** (8%). The latter was characterized as its methyl ester by subsequent esterification ($TMSCHN_2$, MeOH/Et_2O, 0 °C) affording aldehyde ester **14b** in 93% isolated yield. The best conversion was achieved by carrying out ozonization in MeOH, at –78 °C. This resulted in a 77.4% combined yield of a 21.7:1 mixture of *endo*-**12** and *exo*-**13** adduct, separated by chromatography, while the diastereoselectivity of the key hydroxylation reaction was improved and favored **12** (a fivefold raise in **12**:**13** ratio). The abnormal route of oxidation observed on hindered silyl enol ether **11** derived from the bicyclo[2.2.2]octane framework parallels the anomalous ozonization on camphor derived hindered silyloxyalkene reported by Heathcock et al.[17]

The individual isomers could be characterized by NMR techniques; the connectivity in the NMR spectrum was deduced from COSY, HMQC and HMBC experiments, whereas the stereochemical assignments of the resultant bicyclic frameworks of **12** and **13** were based on spatial proximity effects, measured by the 1D NOEDIFF technique on the latter product, which allowed for diagnostic NOEs. Particularly revealing in **13** was the enhancement of the signals due to proton 8β-H (d, δ = 1.55 ppm) upon irradiation of 3-H (d, δ = 3.81 ppm), and vice versa, which indicates the proximity of 3-H and 8β-H. Enhancements were observed in signals corresponding to 1-H (δ = 2.56 ppm) and 8α-H (δ = 1.90 ppm) when 7α-H (δ = 3.98 ppm) was irradiated. Similarly, when 1-H (δ = 2.56) was irradiated enhancement was observed in the signals corresponding to 7α-H and 6α,β-H. On the other hand, enhancement of the signal due to proton 8α-H (δ = 1.90 ppm) and 6α-H (δ = 1.99 ppm) upon irradiation of 5α-H (δ = 3.49 ppm) identified the α-face proton signals, which established that 5α-H, 6α-H, 7α-H, 8α-H are *cis* to each other. This confirmed that minor acyloin **13** was the undesired isomer, while major acyloin **12** was the one hydroxylated from the face opposite to C-5-O*t*Bu.

The stereochemistry at C-3 was also confirmed to be as shown by conversion to orthoester **22** (Scheme 5), to acetonide **28** (Scheme 7), and by X-ray crystallographic analysis of **18b** (vide infra). The latter was obtained by direct alkoxylithiation of **15** (16% isolated yield), along with deacetylated counterpart **18a** (37%) and 28% of recovered starting material. Although of limited preparative interest, this reaction proved beneficial and allowed for the creation of crystalline **18b** which was studied by single-crystal X-ray diffraction analysis (Figure 1); thus, unequivocal stereochemical assignment and further confirmation of the correctness of our previous assignments by NMR techniques (spatial proximity measurements) was enabled.

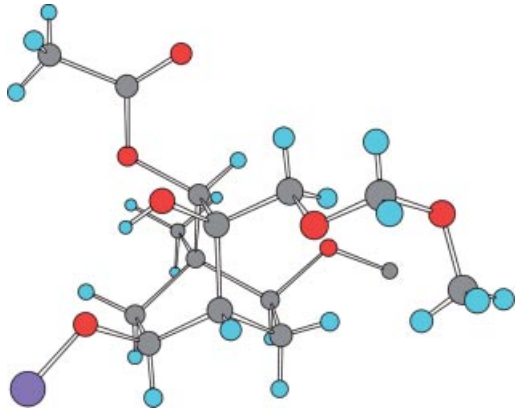
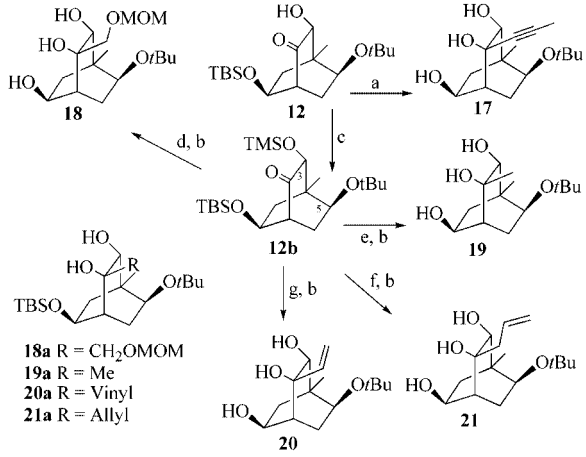


Figure 1. Perspective drawing of the X-ray structure of **18b** (Chem. 3D output from X-ray coordinates; gray, carbon; red, oxygen; cyan, hydrogen; purple, silicon). TBS and *t*Bu protecting groups are simplified for clarity.

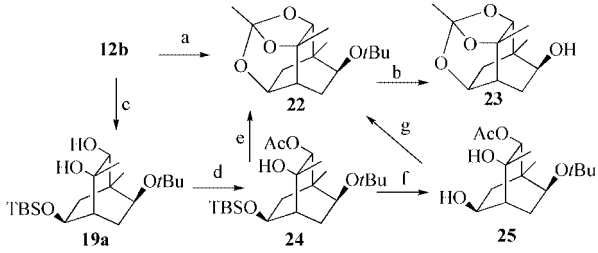
On the basis of these results, the stereochemistries of **12**, **13**, **15**, and **16** were assigned as shown in Scheme 3. A stereodefined construction of tridentate ligands was then carried out with the use of the same nucleophilic partners

as for the bidentate ligands. The operationally simple and straightforward reaction conditions used with **2b**, proved to be successful with **12** as well as with **12b** and **15**. Highly functionalized derivatives **17**–**21** were prepared by nucleophilic addition, which occurred exclusively on the sterically less crowded face, in good to high yields and stereopure (Scheme 4). Reaction of unprotected acyloin **12** with propynyllithium (prepared as above, in situ from propyne, *n*BuLi, HMPA), in dry THF (–78 °C to 25 °C, for 1 h) was completely stereoselective and cleanly afforded desired triol **17** in 72% isolated yield after silica gel chromatography; no detectable amounts of the corresponding TBS-protected diol was observed. Proceeding as above, the reaction between TBS-protected bicyclic aldol **12b** and the α-alkoxyorganolithium derived from Bu_3SnCH_2OMOM by transmetalation with *n*BuL*i* (*n*BuLi, Bu_3SnCH_2OMOM, in dry THF, –78 °C, 20 min) gave a mixture of two products, **18a** and **18** (70% in 2.9:1 ratio) together with unreacted starting material (10%), which were separated by SiO_2 flash chromatography and isolated in their pure forms. Fluoride deprotection, as above, gave desired tridentate ligand **18** in 89% yield. Exposure of **12b** to an excess of MeLi (2.2 M in THF, 5 equiv.) directly afforded **19** in a 90% yield. Again, the ratio **19**:**19a** was variable depending upon the reaction time and temperature; with longer reaction times, more deprotection occurred in the reaction medium, whereas under the optimal conditions (2.2 equiv. of MeLi, dry THF, –78 °C), either bis- or monoprotected triols could be obtained and further transformed by fluoride deprotection (TBAF, 1 h, 60 °C). Vinylmagnesium bromide addition (1 M in dry THF, –78 °C) of either free acyloin **12** (for 1 h at –78 °C, then 2 h at 0 °C; **20a**/**20**, 90% combined yield, 4:1 ratio) or its TMS-protected counterpart **12b** (for 1 h at –78 °C, then overnight at 25 °C; 91% combined of **20a**/**20**, 1:35 ratio) afforded tridentate ligand **20** in high isolated yields following fluoride deprotection. Reaction of bicyclic aldol **12b** with excess allylmagnesium bromide (1 M in Et_2O, 6 equiv.) at –78 °C for 1 h furnished a 95% combined yield of TBS-protected carbinol **21a** along with target tridentate ligand **21**. When the reaction was left overnight at room temperature, a 56% yield of **21a** was obtained along with 22% of **21**. Fluoride deprotection (TBAF, THF) then removed the silyl group, which resisted direct deprotection in the reaction medium to provide **21** in 75% yield. All of the substrates synthesized so far possess a *t*Bu-protected hydroxy group at C-5 in order to afford face selectivity for the C-3 hydroxylation and further chemoselective elaboration for other synthetic uses. In all cases investigated, the nucleophilic addition only occurred on the less hindered face of the carbonyl, and only *exo* adducts were formed. A convenient route to these substrates is shown in Scheme 4.

Suitably protected bicyclic tetraols **17**–**21** with their challenging array of six asymmetric centers, might also serve as attractive building blocks for several synthetic endeavors. Further manipulation of the title compounds should enable the construction of even more elaborated chelating systems since the ligands synthesized in this work could be easily fastened to polymeric supports[18] through the extra hydroxy group at C-5 (arbitrary numbering) or attached to chains that modify their lipohilic/lipophobic character. We thus set out to develop a synthetic route to **23**, by an orthoester-type temporary protection, which allows for such linking endeavors. Targeted orthoester **22** was initially isolated as an unexpected product[19] during the chemical manipulation of **12b** and **25** (Scheme 5). At the outset, the procedure involved the treatment of **12b** with MeLi and the trapping of the resulting alcoholate anion with freshly distilled acetic anhydride to get **24** in a one-pot operation.



Scheme 4. a) Propyne, *n*BuLi, HMPA, –78 °C, to 25 °C. b) TBAF, THF, 60 °C. c) TMS-Im, CH_2Cl_2, 0 °C. d) Bu_3SnCH_2OMOM, *n*BuLi, –78 °C. e) MeLi, THF, –78 °C. f) AllylMgBr, THF, –78 °C. g) VinylMgBr, THF, –78 °C.



Scheme 5. a) MeLi, THF, –78 °C to 0 °C, then Ac_2O, then 35% HCl, 0 °C. b) $BF_3{\cdot}Et_2O$, PhMe, 0 °C. c) MeLi, THF, –78 °C to 0 °C. d) Ac_2O, py, DMAP, 0 °C. e) TBAF, THF, 60 °C (85%) or THF/HCl/H_2O, 0 °C, 50 min (83%). f) TBAF, THF, 0 °C. g) $(CO)_2Cl_2$, DMSO, Et_3N, CH_2Cl_2,–78 °C to 0 °C (80%).

When TMS (acyloin)/TBS (aldol) protected bicyclic framework **12b** was treated with MeLi in THF with the aim to produce **19** after TMS/TBS deprotection (Scheme 5), a mixture of mono and bis-deprotected carbinols was observed before the fluoride deprotection step. This observation was suggestive of an acetic anhydride mediated quenching, which indeed straightforwardly afforded corresponding orthoester **22** in high yield. We then discovered that carbinol acetate **24** is prone to undergo both acid- or fluoride-catalyzed orthoester formation. This was exemplified by the experiments of **24** (TBAF conditions) and **25** (Swern conditions). The one-pot transformation of **12b** into **22** and hence to target **23** is summarized in Scheme 5. Compound **12b** was thus exposed to MeLi in THF at –78 °C for

20 min, and the reaction mixture was warmed to 0 °C. After an additional 20 min stirring at this temperature, the reaction mixture was diluted with THF, Ac_2O was added, and the mixture was quenched with aqueous HCl to afford an 80% isolated yield of the target compound. Orthoester was also formed if **24** was allowed to sit at room temperature in THF in the presence of TBAF overnight (85% isolated yield) or if the latter was treated with HCl/H_2O in THF (83% isolated yield). Thus, fluoride deprotection of **24** furnished **25** when performed at 0 °C for a short time while longer exposure and heating directly gave orthoester **22** in high yield. A single crystal of the latter was grown in CH_2Cl_2/heptane, and an X-ray diffraction study corroborated the structure depicted in Figure 2.

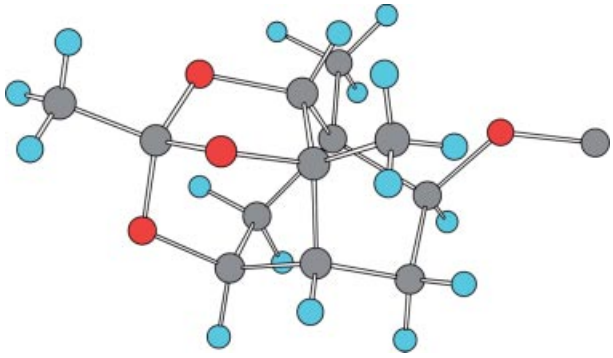
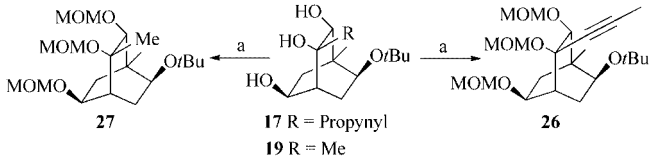


Figure 2. Perspective drawing of X-ray structure of **22** (Chem. 3D output from X-ray coordinates; gray, carbon; red, oxygen; cyan, hydrogen). *t*Bu protecting group is simplified for clarity.

Finally, the latter was also obtained, accidentally though reproducibly, through an attempted Swern oxidation of **25**, aimed at carbonyl formation for use in other synthetic projects. The yield of this transformation is nearly quantitative; triethylamine, although systematically added in the early runs, is not needed. Orthoester **22** proved resistant to AcOH–H_2O, 60 °C for 48 h (only traces of the corresponding diol–acetate was detected), as well as to treatment with *p*-TsOH in MeOH/H_2O for 24 h at 0 °C, reduction with $LiAlH_4$ in THF at 0 °C to room temperature, and reaction with MeLi in THF at –78 °C for 1 h then at room temperature overnight; in those three attempts, unreacted orthoester was recovered.[20] The *t*Bu group was easily cleaved by exposure to $BF_3{\cdot}Et_2O$ in toluene at 0 °C for 45 min, a method developed earlier in our laboratory.[21]

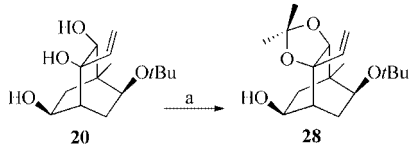
Optically pure tridentate ligands **17** and **19**, obtained in a five step process and high yield from the Hajos–Parrish ketone[22] derived unsaturated diol **1b**, could also serve as precursors for an efficient construction of multidentate ligands, that could be considered as close relatives of supertripodal ligands.[23] Straightforward conversion of **17** and **19** into tris-MOM (methoxymethyl ether) derivatives **26** (75%) and **27** (90% based on recovered starting material), respectively, was accomplished by protection of the triols with the use of chloromethyl methyl ether in the presence of Hünig's base (Scheme 6). Several other multidentate ligands could be easily prepared by appending the suitable functionalities to the pre-existing chelating arms; this leads to a tridimensional framework differing from the one offered by supertripodal ligands.[24]



27 **17** R = Propynyl, **19** R = Me **26**

Scheme 6. a) MOMCl, *i*Pr_2NEt, 25 °C.

The high propensity for orthoester formation[25] of the tridentate ligand precursors constitutes additional proof of the stereochemistry and confirms that all OH groups point towards the same space of the bicyclic framework, which leaves the entering nucleophile and the *t*Bu-protected hydroxy group on the opposite site. Yet, additional proof lies in the ease with which acetonide **28** is formed upon treatment of triol **20** with acetone in the presence of *p*-TsOH at 25 °C; only one out of the two possible isopropylidene alcohols was obtained in 75% isolated yield (Scheme 7). Furthermore, the total 1,2- versus 1,3-diol selectivity observed in acetonide formation could be useful in synthetic endeavors.



20 **28**

Scheme 7. a) *p*-TsOH, 4 Å MS, 0 °C to 25 °C, 6 h (75%).

Conclusions

A central objective associated with the present work was to capitalize on our earlier experience with converting 1,2-unsaturated bicyclic diols of type **1** into the bicyclo[2.2.2]-octane framework of type **2** (Scheme 1). A series of bicyclo[2.2.2]octane derivatives has been prepared for which further applications can be easily imagined. The reported approach combines the advantages of domino reactions with the effortlessness of stereoselective elaboration of bicyclic chiral ligands,[26] in gram quantities. The efficient preparation of 1,3-diols (**6**–**10**) and 1,3,4-triols (**17**–**21**) containing bicyclo[2.2.2]octane frameworks exemplifies this synthetic strategy. The potential of this route to form the bicyclo[2.2.2]octane framework compares favorably with other reported methods by its use of readily available optically pure precursors,[27] mild reaction conditions, high selectivity, and a reasonable number of synthetic steps. We believe the current approach will also be applicable to purposes other than chiral ligand construction, such as stereodefined construction of medium sized rings and hence in the total synthesis of biologically important targets (following paper, this journal).

Experimental Section

General: The term "usual work up" refers to washing the organic layer with brine, drying with anhydrous $MgSO_4$, and evaporating the solvent in vacuo with a rotary evaporator at aspirator pressure. Melting points are uncorrected. IR spectra were recorded with an FTIR instrument through NaCl cell windows. Experimental evidence favoring the structures investigated came from a comprehensive range of ^{1}H- and ^{13}C NMR spectroscopic data (500/125 and 300/75 MHz respectively, 1D and 2D experiments) and corroborated by spatial proximity (n.O.e) studies using mainly the 1D NOEDIFF technique.[28] For all compounds investigated, multiplicities of the ^{13}C NMR spectroscopic resonances were assigned by the SEFT technique.[29] Chemical shifts in the ^{1}H NMR spectra are expressed downfield from TMS with the use of the residual nondeuterated solvent as an internal standard ($CDCl_3$ ^{1}H NMR, 7.26 ppm; C_6D_6 ^{1}H NMR, 7.15 ppm). ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ or the C_6D_6 triplet centered at δ = 77.0 ppm and 128.0 ppm, respectively. Mass spectra acquired in the positive ion mode under electron spray ionization (ES^+) using a mobile phase of methanol, will be abbreviated as ESIMS (MeOH). HR will be added for the high resolution mass measurements (HRESIMS).

CCDC-610968 (**18b**), and CCDC-611342 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

7-*tert*-Butoxy-1-methyl-3-prop-1-ynylbicyclo[2.2.2]octane-2,3,5-triol (17): To a solution of propyne in dry THF (2 mL) at –78 °C under an argon atmosphere, *n*BuLi (1.6 M, 1.46 mL, 2.34 mmol, 8 equiv.) was added dropwise. The mixture was warmed to –15 °C and stirring was continued at this temperature. After 2 h, HMPA (0.3 mL) was added at –20 °C, and the resulting mixture was stirred for 10 min. A solution of **12** (100 mg, 0.29 mmol, 1 equiv.) in THF (1 mL) and HMPA (0.3 mL) was then added at –30 °C, and the mixture was left to stir overnight at room temperature, diluted with diethyl ether, quenched with sat NH_4Cl and worked up as usual. The residue was purified by chromatography (heptane/EtOAc, 1:1) to give **17** (58 mg, 72%). $[\alpha]_D^{20}$ = 88 (c 0.9, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3324, 2972, 2360, 2335, 1449, 1363, 1192, 1094, 1065, 994, 971, 668 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (s, 3 H), 1.12 (s, 9 H), 1.64 (m, 3 H), 1.86 (s, 3 H), 1.90 (m, 1 H), 2.15 (m, 1 H), 3.26 (dd, *J* = 5.6, 9.4 Hz, 1 H), 3.78 (td, *J* = 1.9, 8.5 Hz, 1 H), 3.98 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.6, 19.5, 28.7, 33.7, 35.8, 38.7, 43.7, 69.4, 70.4, 71.0, 72.6, 73.0, 79.1, 82.9 ppm. ESIMS (MeOH): *m*/*z* (%) = 305.1 (100) [M + Na]$^+$. HRESIMS: calcd. for $C_{16}H_{26}O_4Na$ 305.1729; found 305.1730. $C_{16}H_{26}O_4$ (282.18): calcd. C 68.06, H 9.28; found C 67.66, H 9.22.

7-*tert*-Butoxy-1,3-dimethylbicyclo[2.2.2]octane-2,3,5-triol (19): To a stirred solution of **12b** (200 mg, 0.46 mmol) in THF (6 mL) at –78 °C was added methyl lithium (2.2 M in THF, 0.46 mL, 2.2 equiv.). The reaction was kept at –78 °C for 30 min, warmed up to 0 °C, and left to react for a further 45 min. After complete consumption of the starting material, a solution of HCl (4 N) was added, the mixture was left to react at room temperature for another 20 min, neutralized by the addition of a saturated solution of $NaHCO_3$, extracted 3 times with EtOAc, and worked up as usual. The crude residue was purified by chromatography over silica gel (heptane/EtOAc, 1:1) to provide tridentate ligand **19** (110 mg, 90%) as a white solid. $[\alpha]_D^{20}$ = +123 (*c* = 1.05, $CHCl_3$). M.p. 134–135 °C. IR (film): $\tilde{\nu}$ = 3324, 2964, 2927, 1451, 1366, 1208, 1136, 1074, 1033, 1000, 926, 815 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 3 H), 1.10 (s, 9 H), 1.32 (s, 3 H), 1.44 (dt, *J* = 4.2, 15.9 Hz, 1 H), 1.56 (ddd, *J* = 1.8, 9.6, 14.3 Hz, 1 H), 1.65 (dd, *J* = 6.0, 14.3 Hz, 1 H), 1.80 (m, 1 H), 1.81 (ddd, *J* = 3.8, 9.0, 15.9 Hz, 1 H), 2.95 (br. s, 1 H), 3.25 (dd, *J* = 4.3, 9.0 Hz, 1 H), 3.56 (br. s, 1 H), 3.64 (br. s, 1 H), 3.83 (m, 1 H), 4.51 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9, 27.9, 28.7, 34.3, 35.6, 39.1, 42.9, 70.7, 70.8, 72.0, 73.0, 73.1 ppm. ESIMS (MeOH): *m*/*z* = 281.1 [M + Na]$^+$. HRESIMS: calcd. for $C_{14}H_{26}O_4Na$ 281.1729; found 281.1731. $C_{14}H_{26}O_4$ (258.18): calcd. C 65.09, H 10.14; found C 64.78, H 9.83.

Preparation of Multidentate Ligands in the Form of Tris-MOM Protected Triols - 7-*tert*-Butoxy-2,3,5-trimethoxymethoxy-1-methyl-3-prop-1-ynylbicyclo[2.2.2]octane (26): To a stirred solution of **17** (40 mg, 0.14 mmol) in dry dichloromethane (1 mL) was added *i*Pr_2Net (0.24 mL, 0.15 mmol, 6.2 equiv.) followed by the addition of MOMCl (0.06 mL, 0.84 mmol, 6 equiv.). The mixture was stirred at room temperature overnight, quenched with water, and extracted with dichloromethane. The combined extracts were washed with hydrochloric acid (1 N), worked up as usual, and chromatographed on silica gel (heptane/EtOAc, 2:1) to yield 45 mg (75%) of **26**. $[\alpha]_D^{20}$ = +166 (*c* 1.20, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2966, 2928, 2838, 2816, 1387, 1361, 1191, 1149, 1107, 1072, 1038, 995, 917 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (s, 3 H), 1.13 (s, 9 H), 1.50 (ddd, *J* = 1.8, 9.8, 13.2 Hz, 1 H), 1.70 (ddd, *J* = 1.7, 6.8, 15.7 Hz, 1 H), 1.88 (s, 3 H), 1.86–1.96 (m, 2 H), 2.05 (td, *J* = 1.8, 4.7 Hz, 1 H), 3.28 (dd, *J* = 5.8, 9.3 Hz, 1 H), 3.33 (s, 3 H), 3.43 (s, 3 H), 3.44 (s, 3 H), 3.73 (t, *J* = 8.5 Hz, 1 H), 4.09 (d, *J* = 1.7 Hz, 1 H), 4.56 and 4.59 (ABquart, *J* = 6.8 Hz, 2 H), 4.71 and 5.06 (ABquart, *J* = 6.4 Hz, 2 H), 4.94 and 4.96 (ABquart, *J* = 5.9 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 3.7, 20.4, 28.8, 33.1, 34.8, 38.9, 42.0, 55.2 55.9, 56.2, 70.4, 72.8, 72.9, 73.7, 77.7, 81.4, 81.7, 93.0, 94.7, 95.9 ppm. ESIMS (MeOH): *m*/*z* (%) = 437.2 (100) [M + Na]$^+$. HRESIMS: calcd. for $C_{18}H_{38}O_7Na$ 437.2515; found 437.2509. $C_{22}H_{38}O_7$ (414.26): calcd. C 60.80, H 8.70; found C 60.61, H 8.35.

7-*tert*-Butoxy-2,3,5-trimethoxymethoxy-1,3-dimethylbicyclo[2.2.2]-octane (27): Proceeding as above, to **19** (60 mg, 0.23 mmol) in dry dichloromethane (2 mL) was added *i*Pr_2Net (0.24 mL, 1.42 mmol, 6.2 equiv.) followed by the addition of MOMCl (0.1 mL, 1.38 mmol, 6 equiv.). The mixture was stirred at room temperature overnight after addition of excess MOMCl, quenched with water, and extracted with dichloromethane. The combined extracts were washed with hydrochloric acid (1 N), worked up as usual and chromatographed on silica gel (heptane/EtOAc, 2:1) to yield quantitatively **27**. $[\alpha]_D^{20}$ = +201 (c 0.35, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2971, 2928, 1727, 1389, 1364, 1145, 1110, 1093, 1039, 919 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 1.10 (s, 9 H), 1.40 (ddd, *J* = 2.3, 4.8, 14.3 Hz, 1 H), 1.48 (s, 3 H), 1.48 (m, 1 H), 1.88 (ddd, *J* = 4.5, 9.4, 14.0 Hz, 1 H), 1.97 (m, 2 H), 3.26 (dd, *J* = 4.8, 9.3 Hz, 1 H), 3.33 (s, 3 H), 3.41 (s, 3 H), 3.45 (s, 3 H), 3.64 (s, 1 H), 3.69 (t, *J* = 8.5 Hz, 1 H), 4.55 and 4.58 (ABquart, *J* = 6.7 Hz, 2 H), 4.59 and 4.92 (ABquart, *J* = 8.0 Hz, 2 H), 4.74 and 4.85 (ABquart, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 26.0, 28.7, 33.3, 35.4, 39.6, 39.8, 55.1, 55.5, 55.8, 70.7, 72.9, 73.9, 76.4, 78.8, 92.0, 94.6, 97.0 ppm. ESIMS (MeOH): *m*/*z* (%) = 413.2 (100) [M + Na]$^+$. HRESIMS: calcd. for $C_{20}H_{38}O_7Na$ 413.2515; found 413.2508. $C_{20}H_{38}O_7$ (390.5): calcd. C 61.51, H 9.81; found C 61.96, H 9.61.

Supporting Information (see footnote on the first page of this article): Procedures for the synthesis and spectral characterization for all compounds including structural analysis of **18b** and **22**.

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