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Synthesis of Bicyclo[3.1.0]hexanes Functionalized at the Tip of the Cyclopropane Ring. Application to the Synthesis of Carbocyclic Nucleosides

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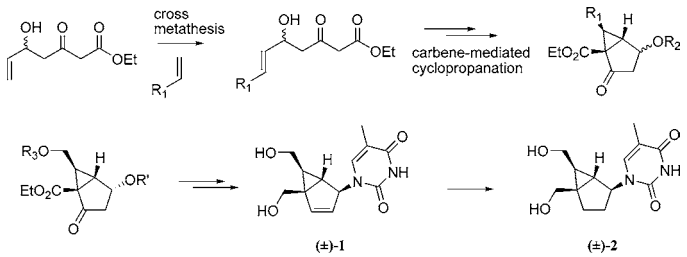
ABSTRACT



A general synthetic strategy for the preparation of functionalized bicyclo[3.1.0]hexanes is described. The new approach employs a cross metathesis step designed to functionalize the appropriate terminal olefin of the bicyclo[3.1.0]hexane precursor and a carbene-mediated intramolecular cyclopropanation reaction on the corresponding diazo intermediate. This combined methodology allowed the diastereoselective introduction of chemically diverse substituents at the tip of the cyclopropane group, except in cases where the substituents consisted of electron-withdrawing groups where a competing [3 + 2] cycloaddition predominated.

To further explore structure−activity relationships on bicyclo-[3.1.0]hexane nucleosides by functionalizing the tip of the cyclopropane ring, the majority of published chemical approaches appeared unsuitable,[1] except for the intramolecular carbene-mediated cyclopropanation approach recently developed in our laboratory.[2,3] This versatile reaction has been successfully applied to the synthesis of optically active bicyclo[3.1.0]hexane nucleosides using various approaches such as starting with chiral compounds,[4] employing chiral auxilaries,[5] and even incorporating chemico-enzymatic steps.[2,3] On the other hand, relatively few examples describing the use of chiral catalysts for the intramolecular cyclopropanation of diazoketoesters have been reported, and the level of enantiocontrol achieved has been rather low.[6]

With the aim of developing a general strategy for the synthesis of bicyclo[3.1.0]hexanes substituted at the tip of

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(3) Yoshimura, Y.; Moon, H. R.; Choi, Y.; Marquez, V. E. *J. Org. Chem.* **2002**, *67*, 5938.

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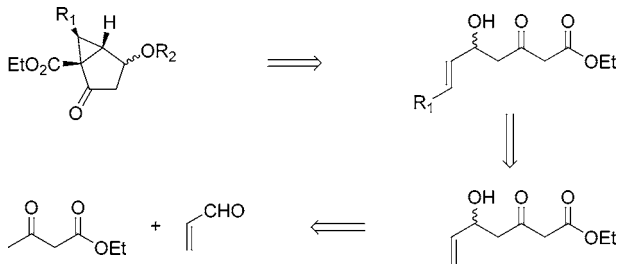
the cyclopropane ring, the use of a cross metathesis[7] reaction was envisioned (Scheme 1). The mild conditions and

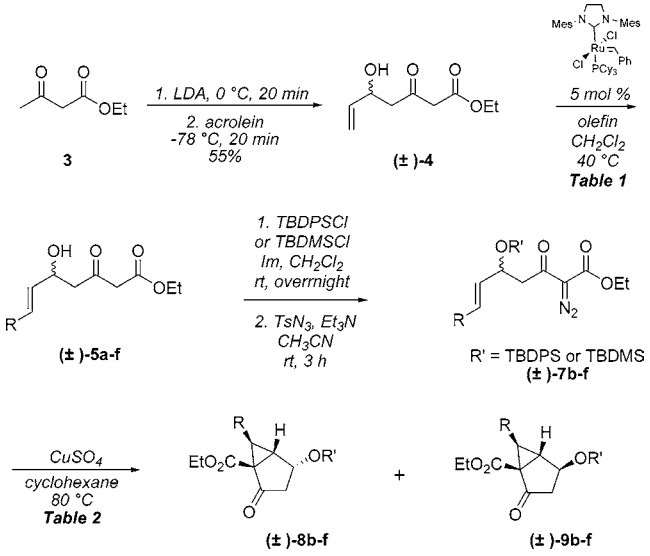
Scheme 1



functional group tolerance of modern cross metathesis methodologies were expected to allow the introduction of chemically diverse substituents at the terminal olefin of the bicyclo[3.1.0]hexane precursor. Then, an ensuing intramolecular cyclopropanation reaction on the corresponding diazo intermediate was anticipated to complete the formation of the desired template. This combined methodology allowed the diastereoselective introduction of chemically diverse substituents at the tip of the cyclopropane ring, except in cases where the substituents consisted of electron-withdrawing groups where a competing [3 + 2] cycloaddition predominated.

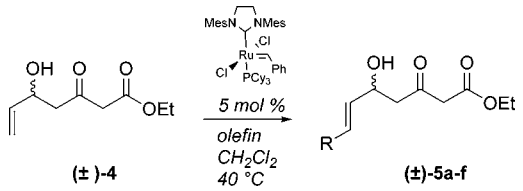
The substrate for the cross metathesis reaction was prepared from ethyl acetoacetate (**3**) and acrolein as described in Scheme 2.[2] With intermediate (±)-**4** at hand, we initiated

Scheme 2



studies on the cross metathesis reaction. We found out that free allylic alcohol (±)-**4** reacted smoothly with most olefin

Table 1. Cross Metathesis



entry	product	R	time (h)	yield (%)[d]
1	**5a**	CH_2OAc[a,b]	20	70
2	**5b**	CH_2OBn[a,b]	18	90
3	**5c**	$Si(OEt)_3$ [c]	2	98
4	**5d**	$CH_2P(O)(OEt)_2$ [c]	16	88
5	**5e**	$P(O)(OEt)_2$ [c]	48	47
6	**5f**	CO_2CH_3 [b]	5	95

[a] The dimeric olefin was used as cross partner. [b] 2 equiv of cross partner olefin were employed. [c] 5 equiv of cross partner olefin were employed. [d] The *trans* isomer was the only one detected in all cases.

cross partners in the presence of either 2nd generation Grubbs[8] or Hoveyda−Grubbs[9] catalysts (Table 1) to afford the corresponding disubstituted olefins with excellent *E*-selectivity and in high yields as mixtures of keto−enol tautomers.[10] In contrast, when the hydroxyl group was protected as an acetate or as a silyl ether, no cross metathesis reaction was observed and starting material was recovered (data not shown). As has already been observed by other groups using different substrates,[11] the size of the allylic substituent strongly modulates the outcome of the cross metathesis reaction.

Our initial efforts focused on elaborating the terminal olefin to the corresponding allylic alcohol derivatives (entries 1 and 2). In these cases, the use of symmetric internal olefins was found to be more efficient than simply using prop-2-enyl acetate or 1-(phenylmethoxy)prop-2-ene.[12] Reaction with triethoxyvinylsilane (entry 3) was quantitative and fast.[13] When olefin (±)-**4** was treated with diethoxyallylphosphonate, the cross product (±)-**5d** was obtained stereoselectively and in very good yield (88%, entry 4). On the other hand, reaction with diethoxyphosphinovinyl-1-one yielded the desired olefin in low yield (47%, entry 5),[14] probably due to its very low reactivity in cross metathesis reactions (no homodimerization).[15] Finally, reaction with methylacrylate produced the desired olefin in high yield (entry 6).

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(10) ^1H and ^{13}C NMR experiments show that a small amount of the enol tautomer is always present in solution (see Supporting Information).

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(14) In this case, 50% of starting material (±)-**4** was recovered.

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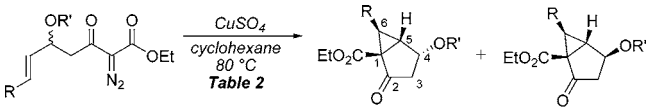
Cross metathesis products (±)-**5a**−**f** were further elaborated into the olefin-ketocarbene cyclopropanation substrates (±)-**7b**−**f** by protection of the free allylic hydroxyl group as silyl enol ethers (excellent to quantitative yields) followed by diazo transfer with *p*-toluenesulfonyl azide also in quantitative yields (Scheme 2).[3] These intermediates were stirred at 80 °C employing cyclohexane as solvent in the presence of copper sulfate[16] to generate the desired bicyclic systems as chromatographically separable mixtures (see Supporting Information) of diastereomers favoring the α isomer (±)-**8** over the *β* isomer (±)-**9** in good to excellent yields (Table 2, entries 1−3).

Table 2. Carbene-Mediated Intramolecular Cyclopropanation



(±)-7b-f (±)-8b-f (±)-9b-f

entry	product	R	time (h)	yield (%), (*endo*/*exo*)
1	**8b/9b**[a]	CH_2OBn	41	75 (2.2/1)
2	**8c/9c**[b]	$Si(OEt)_3$	22	62 (4/1)
3	**8d/9d**[a]	$CH_2P(O)(OEt)_2$	22	95 (3.3/1)
4	**8e/9e**[a]	$P(O)(OEt)_2$	48	0
5	**8f/9f**[a]	CO_2CH_3	48	18 (1/1)

[a] R′ = TBDPS; [b] R′ = TBDMS.

As previously reported, the stereochemical outcome of the reaction can be rationalized in terms of steric hindrance assuming that the transition state adopts a product-like pseudoboat conformation.[3] The rigid boat conformation of the bicyclo[3.1.0]hexane system, which for this class of compounds has been extensively confirmed by X-ray crystallography and NMR analysis,[1c,d,17] makes the assignment of the stereochemistry particularly straightforward. For example, in intermediate (±)-**8b**, H-4 appears as a doublet of doublet of doublets (J = 8.4, 7.4, and 5.3 Hz). On the other hand, when H-4 is α, as in intermediate (±)-**9b**, the signal appears as a doublet (J = 4.9 Hz). In the latter case, two of the three dihedral angles with vicinal protons are close to 90° so their coupling constants approach zero. Both relative configurations of C-4 and C-6 were validated by the X-ray structure of the final product (±)-**2** (Figure 1).

The reaction outcome was completely different when the starting olefin was substituted with electron-withdrawing groups, such as componds (±)-**7e,f** (Table 2, entries 4 and 5). In those cases, a noncatalyzed intramolecular 1,3-dipolar cycloaddition pathway predominated over the carbene-mediated cyclopropanation, and consequently bicyclic pyrazoline products (±)-**10e,f** and (±)-**11f** were prevalent over

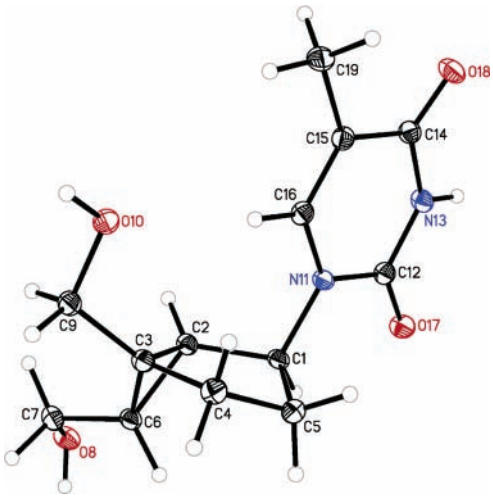
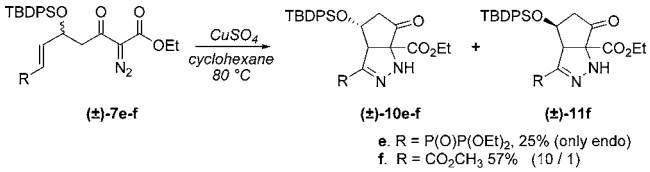


Figure 1. Crystal structure of (±)-**2**. Displacement ellipsoid plot drawn at the 50% probability level. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and has been allocated the deposition number CCDC 295062.

the bicyclo[3.1.0]hexane system (Scheme 3). This 1,3-dipolar addition of diazo compounds and α,*β*-unsaturated olefins is well documented in the literature.[18]

Scheme 3



The developed methodology was applied to the synthesis of carbocyclic nucleosides (±)-**1** and (±)-**2**. Bicyclic compound (±)-**8b** was used as starting material, and a convergent approach through a Mitsunobu-type[19] coupling was chosen to assemble the target nucleoside. Compound (±)-**8b**, which was prepared on a 10 g scale with the same yield reported in Tables 1 and 2, was reduced in a stepwise fashion by first reducing the keto group with sodium borohydride and then the ester by treatment with lithium aluminum hydride to afford diol (±)-**13** in 75% overall yield (Scheme 4).[2] After selective benzoylation of the primary hydroxyl group, the secondary alcohol was replaced by iodine with retention of configuration (double inversion)[1e] to yield intermediate (±)-**15**. Compound (±)-**15** was subjected to elimination conditions to generate intermediate (±)-**16**, which after deprotection of the secondary hydroxyl group yielded the Mitsunobu coupling precursor (±)-**17**.

(16) $CuSO_4$ was employed as catalyst because it gave better diastereoisomeric ratios of α (±)-**8**/*β* (±)-**9** in comparison to other catalysts, such as $Rh_2(OAc)_4$, $Cu(OTf)$ or $Cu(acac)_2$, on this class of substrates (Moon, H. R.; Marquez, V. E. Unpublished results).

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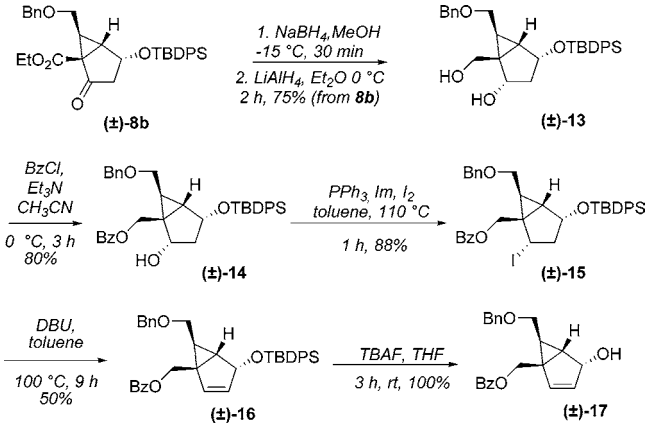
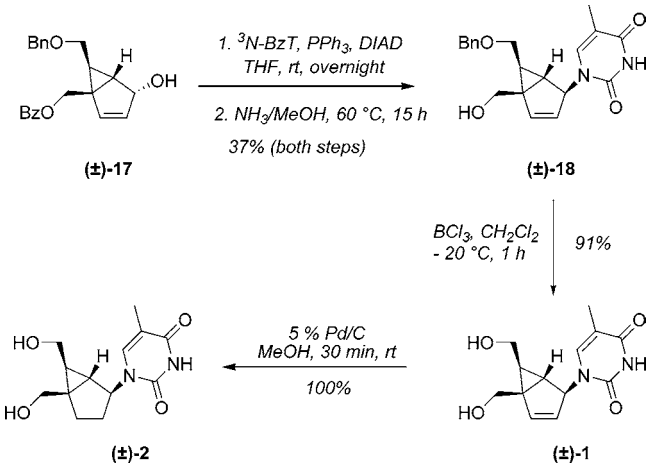
Scheme 4



Scheme 5



As shown in Scheme 5, treatment of compound (±)-**17** under Mitsunobu conditions employing ^3N-benzoylthymine[20] as nucleophile yielded, after hydrolysis of the benzoyl groups, nucleoside precursor (±)-**18** in 37% overall yield.

The benzyl protecting group was then cleaved by treatment with boron trichloride at low temperature to afford nucleoside analogue (±)-**1** in high yield. Hydrogenation of the double bond proceeded smoothly to give the thymidine analogue (±)-**2** in quantitative yield.

This newly synthesized analogue provided adequate crystals for X-ray analysis, and the crystal structure (Figure 1) validated all of the spectral assignments as well as the base disposition (*anti*) and the pseudoboat conformation of the carbocyclic ring.

In conclusion, we have developed a general strategy for the synthesis of bicyclo[3.1.0]hexanes substituted at the tip of the cyclopropane ring, employing simple starting materials. The synthetic potential of this strategy has been demonstrated by the synthesis of carbocyclic nucleoside analogues (±)-**1** and (±)-**2**. The remarkable growth in the area of asymmetric transition-metal-catalyzed cyclopropanation reactions during the past few years[21] bodes well for the idea of attempting a catalytic asymmetric version of the synthetic approach presented here. Future investigations on these attempts will be published in due course.

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Supporting Information Available: Experimental procedures and characterization data for all intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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