One-Pot Base-Promoted Tandem Michael Addition–Intramolecular Aldolization. Stereoselective Synthesis and Reactivity of 2-Hydroxybicyclo[3.2.1]octan-8-ones

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α-Substituted cyclopentanones **1** react with α,β-unsaturated aldehydes **2** by a facile base-promoted (K_2CO_3, Cs_2CO_3, DBU) tandem Michael addition–intramolecular aldol cyclization to give, in synthetically useful yields (30–99%), highly substituted, stereodefined and optically active 2-hydroxybicyclo[3.2.1]octan-8-ones **3–19**. A generally separable mixture of isomers, in which the one bearing an equatorial hydroxy group predominates, is obtained with simple aldehydes. In the case of prostereogenic Michael acceptors one diastereomer usually prevails from as little as 75% to as much as >97%. This high axial-C-4 stereoselectivity results from a diastereoselective Michael addition and can be easily reversed by simple adaptation of the reaction conditions. The structures of the products rest upon NMR spectroscopy and chemical transformations. The synthetic potential of hydroxybicyclo[3.2.1]octanes is illustrated by transformations of **25–28**, especially by their facile conversion to functionalized and stereodefined cycloheptanes **30**, **32**, **35–42**.

Introduction

The stereoselective formation of the bicyclo[3.2.1]-octane skeleton has received much attention since this structure represents the basic framework of numerous biologically active natural products.[1] Among the various strategies encountered in the literature, the ring expansion of a [2.2.1] intermediate was one of the first.[2] The rearrangement of bicyclo[2.2.2]octanes,[3] the ring contraction of [3.3.1] derivatives,[4] the selective fragmentation of bi- and tricyclic intermediates,[5] and the solvolytic cyclization of functionalized cycloheptenes[6] have also been used successfully during the syntheses of a number of natural compounds. The following general strategies have also been used: the aldol condensation,[7] the intramolecular Wittig olefination,[8] the Diels–Alder reaction[9] or other electrocyclizations,[10] the cobalt catalyzed [2 + 2 + 2] cycloaddition[11] or the ene-reaction of acetylenic β-keto esters,[12] and the photochemical-induced rearrangement of ethylenic cycloalkanones.[13] Intramolecular carbon–carbon bond formation[14] including the pinacolic coupling,[15] Michael addition,[16] Reformatsky[17] and Dieckmann condensations,[18] intramolecular radical carbocyclization,[19] and finally the use of organometallic intermediates[20] have been used quite often in the preparation of the [3.2.1]octane skeleton, and many interesting synthetic applications are reported. Another approach

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(1) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White C. T. *The Total Synthesis of Natural Products*; Apsimon, J. W., Ed.; Wiley: New York, 1982, Vol. 5. Hanson, J. R. *Terpenoids and Steroids*, a Specialist Periodical Report; The Royal Society of Chemistry: London, 1983; Vol. 12, p 195. Yamamura, S.; Shizuri, Y.; Shigemori, H.; Okuno, Y.; Ohkubo, M. *Tetrahedron* **1991**, *47*, 635. Mander, L. N. *Chem. Rev.* **1992**, *92*, 573. Engler, T. A.; Wei, D. D.; Letavic, M. A. *Tetrahedron Lett.* **1993**, *34*, 1429. Nakajima, H.; Isomi, K.; Hamasaki, T.; Ichinoe, M. *Tetrahedron Lett.* **1994**, *35*, 9597.

(2) Jefford, C. W. *Proc. Chem. Soc.* **1963**, 64. Ghosez, L.; Laroche, P. *Proc. Chem. Soc.* **1963**, 90. Moore, W. R.; Moser, W. R.; LaPrade, J. E. *J. Org. Chem.* **1963**, *28*, 2200. De Selms, R. C.; Combs, C. M. *J. Org. Chem.* **1963**, *28*, 2206. Bergman, E. *J. Org. Chem.* **1963**, *28*, 2210. Sisti, A. J. *Tetrahedron Lett.* **1967**, *8*, 5327. Patel, V.; Ragauskas, A. J.; Stothers, J. B. *Can. J. Chem.* **1986**, *64*, 1440. Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956. Hsu, L. F.; Chang, C. P.; Li, M. C.; Chang, N. C. *J. Org. Chem.* **1993**, *58*, 4756. Djuardi, E.; Bovonsombat, P.; Mc Nelis, E. *Tetrahedron* **1994**, *50*, 11793.

(3) Monti, S. A.; Dean, T. R. *J. Org. Chem.* **1982**, *47*, 2681. Van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142. Uyehara, T.; Osanai, K.; Sugimoto, M.; Suzuki, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 7264. Shanker, P. S.; Rao, G. S. R. S. *J. Chem. Soc., Chem. Commun.* **1994**, 621.

(4) Kraus, G. A.; Hon, Y. S.; Sy, J. *J. Org. Chem.* **1986**, *51*, 2625.

(5) Beames, D. J., Mander, L. N. *J. Chem. Soc., Chem. Commun.* **1969**, 498. Mori, K. *Tetrahedron* **1971**, *27*, 4907. Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem. Res.* **1974**, *7*, 106. Ghatak, U. R.; Alam, S. K.; Chakraborti, P. C.; Ranu, B. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1669. Yanagiya, M.; Kaneko, K.; Kaji, T.; Matsumoto, T. *Tetrahedron Lett.* **1979**, 1761. Barker, A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1901. Narasaka, K. Shimadzu, H.; Hayashi, Y. *Chem. Lett.* **1993**, 621. Sagawa, S.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1994**, *35*, 603. Hadjiarapoglou, L.; de Meijere, A.; Seitz, H. J.; Klein, I.; Spitzner, D. *Tetrahedron Lett.* **1994**, *35*, 3269.

(6) Cope, A. C.; Nealy, D. L.; Scheiner, P.; Wood, G. *J. Am. Chem. Soc.* **1965**, *87*, 3130 and references cited therein.

(7) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1965**, *87*, 5728. Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Oplinger, J. A.; Dike, M. S. *J. Am. Chem. Soc.* **1984**, *106*, 4558. Utaka, M.; Fujii, Y.; Takeda, A. *Chem. Lett.* **1985**, 1123. Yamamoto, T.; Eki, T.; Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron* **1992**, *48*, 4517. Lohray, B. B.; Zimbiniski, R. *Tetrahedron Lett.* **1990**, *31*, 7273. Bull, J. R. *Synlett* **1994**, 709.

(8) Bestmann, H. J.; Schade, G. *Tetrahedron Lett.* **1982**, *23*, 3543. Dauben, W. G.; Ipaktschi, J. *J. Am. Chem. Soc.* **1973**, *95*, 5088.

(9) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, 48, 1147. Rigby, J. H.; Kotnis, A. S. *Tetrahedron Lett.* **1987**, *28*, 4943. Aubert, C.; Gotteland, J. P.; Malacria, M. *J. Org. Chem.* **1993**, *58*, 4298.

(10) Büchi, G.; Chu, P. S. *Tetrahedron* **1981**, *37*, 4509. Funk, R. L.; Horcher, L. H. M.; Daggett, J. U.; Hansen, M. M. *J. Org. Chem.* **1983**, *48*, 2632. Joshi, N. N.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1986**, *27*, 687. Mayr, H.; Bäuml, E.; Cibura, G.; Koschinsky, R. *J. Org. Chem.* **1992**, *57*, 768. Markò, I. E.; Seres, P.; Evans, G. R.; Swarbrick, T. M. *Tetrahedron Lett.* **1993**, *34*, 7305. Davies, H. M. L.; Peng, Z. Q.; Houser, J. H. *Tetrahedron Lett.* **1994**, *35*, 8939. Oh, J.; Lee, J.; Jin, S. J.; Cha, J. K. *Tetrahedron Lett.* **1994**, *35*, 3449. Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23.

(11) Germanas, J.; Aubert, C.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 4006.

(12) Stammler, R.; Malacria, M. *Synlett* **1994**, 92.

(13) Heidbreder, A.; Mattay, J. *Tetrahedron Lett.* **1992**, *33*, 1973. Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1992**, *114*, 1824.

(14) Bailey, D. M.; Bowers, J. E.; Gutsche, C. D. *J. Org. Chem.* **1963**, *28*, 610. Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 288. Whitesell, J. K.; Matthews, R. S.; Solomon, P. A. *Tetrahedron Lett.* **1976**, 1549. Heumann, A.; Krauss, W. *Tetrahedron* **1978**, *34*, 405. Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3297.

(15) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260. Arseniyadis, S.; Yashunsky, D. V.; Pereira de Freitas, R.; Muñoz Dorado, M.; Toromanoff, E.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 1137.

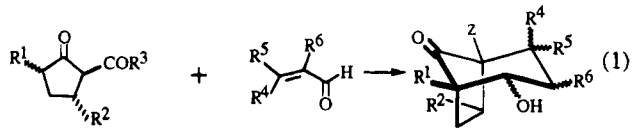
0022-3263/95/1960-6872$09.00/0

is the α,α′-annelation of ketones by the tandem alkylation–Michael addition of enamines,[21] which has recently been improved by using the reactivity of nitroallylic esters.[22]

Bicyclo[3.2.1]octanes can also serve as useful intermediates,[23] in fragmentations leading to cycloheptanes,[24] as in the well-known Stork–Landesman procedure,[25] which involves a 2-amino-substituted bicyclo[3.2.1]octan-8-one intermediate. More recent examples involving 2-oxy substituted bicyclo[3.2.1]octan-8-ones are the acetalization of cyclopentanones with a carbonyl function at the C-3-position of an α-side chain,[26] the preparation of 2-methylcycloheptan-1,5-dione,[27] the synthesis of *trans*-hydroazulenes,[28] and our recent one-pot two-carbon ring expansion of α-carbonyl substituted cyclopentanones.[29]

However, in spite of the synthetic usefulness of this system, few reports deal with the one-pot preparation of these bicyclic compounds from simple intermediates. The high pressure-induced tandem Michael addition–intramolecular aldolization of β-keto esters with α,β-unsaturated ketones[30] and the annulation of β-keto thiolesters[31] or β-keto sulfones[32] constitute the three major examples.

It is the purpose of this paper to describe, in full detail, the scope and limitations of a new stereoselective one-pot access to the valuable 2-hydroxybicyclo[3.2.1]octan-8-one ring system. We also present some aspects of its reactivity for the preparation of stereodefined cycloheptane derivatives. Our approach is based on a one-pot base-promoted tandem Michael addition–intramolecular aldol cyclization of β-dicarbonyl derivatives **1** with α,β-unsaturated aldehydes **2**. The method allows the preparation of highly substituted, stereodefined, and optically active hydroxybicyclo[3.2.1]octanones with up to five stereogenic centers under extremely simple and very mild conditions (eq 1).[33]



(1)

1a: $R^1 = R^2 = H$, $R^3 = OMe$
b: $R^1 = Me$, $R^2 = H$, $R^3 = OMe$
c: $R^1 = H$, $R^2 = Me$, $R^3 = OMe$
d: $R^1 = H$, $R^2 = Me$, $R^3 = OtBu$
e: $R^1 = H$, $R^2 = Me$, $R^3 = OBn$
f: $R^1 = R^2 = H$, $R^3 = Me$

2a: $R^4 = R^5 = R^6 = H$
b: $R^4 = R^6 = H$, $R^5 = Me$
c: $R^4 = R^5 = Me$, $R^6 = H$
d: $R^4 = R^5 = H$, $R^6 = Me$
e: $R^4 = R^6 = H$, $R^5 = nPr$
f: $R^4 = H$, $R^5 = Et$, $R^6 = Me$
g: $R^4 = H$, $R^5, R^6 = -(CH_2)_4-$
h: $R^4 = R^6 = H$, $R^5 = Ph$
i: $R^4 = R^6 = H$, $R^5 = o$-tolyl
j: $R^4 = R^6 = H$, $R^5 = $ furyl

3-19 (Z = COR^3)

Results and Discussion

The results of our study on the base-promoted tandem Michael addition–aldol cyclization are reported in Tables 1 and 2. Our one-pot condensative cyclization takes place under very mild conditions by reaction of α-carbonyl substituted cyclopentanones **1a–f** with α,β-unsaturated aldehydes **2a–j** at room temperature in the presence of 1.5 equiv of base. The reaction is quite general and proceeds smoothly to give, in synthetically useful yields and with good selectivity, 2-hydroxybicyclo[3.2.1]octanones **3–19**. To our knowledge, there is no previous example of the direct construction of a bicyclo[3.2.1]octane, starting with simple α,β-unsaturated aldehydes and α-carbonyl cyclopentanones,[34] probably due to the difficulty in

(16) Danishefsky, S.; Koppel, G.; Levine, R. *Tetrahedron Lett.* **1968**, *9*, 2257. Nagata, W.; Wakabayashi, T.; Narisada, M.; Hayase, Y.; Kamata, S. *J. Am. Chem. Soc.* **1971**, *93*, 5740. Trost, B. M.; Shuey, C. D.; DiNinno, F.; McElvain, S. S., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284. Pearson, A. J. *Tetrahedron Lett.* **1980**, *21*, 3929. For examples using the intramolecular double Michael addition see, Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010. Ghera, E.; Ramesh, N. G.; Laxer, A.; Hassner, A. *Tetrahedron Lett.* **1995**, *36*, 1333.

(17) Corey, E. J.; Narisada, M.; Hiraoka, T.; Ellison, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 396. Ziegler, F. E.; Condon, M. E. *J. Org. Chem.* **1971**, *36*, 3707.

(18) Baker, A. J.; Goudie, A. C. *J. Chem. Soc., Chem. Commun.* **1971**, 180. Selvakumar, N.; Rao, G. S. R. S. *Tetrahedron Lett.* **1993**, *34*, 7789.

(19) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871. Srikrishna, A.; Hemamalini, P. *J. Org. Chem.* **1990**, *55*, 4883. Berkowitz, W. F.; Wilson, P. J. *J. Org. Chem.* **1991**, *56*, 3097. Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607. Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 322. Curran, D. P.; Yoo, B.; *Tetrahedron Lett.* **1992**, *33*, 6931. Weinges, K.; Reichert, H.; Huber-Patz, U.; Irngart-Inger, H. *Liebigs Ann. Chem.* **1993**, *4*, 403. Ozaki, S.; Horiguchi, I.; Matsushita, H.; Ohmori, H. *Tetrahedron Lett.* **1994**, 35, 725.

(20) Kende, A. S.; Roth, B; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808. Barbero, A.; Cuadrado, P.; Gonzàlez, A. M.; Pulido, F. J.; Rubio, R.; Fleming, I. *Tetrahedron Lett.* **1992**, *33*, 5841. Yeh, M. C. P.; Sheu, B. A.; Fu, H. W.; Tau, S. I.; Chuang, L. W. *J. Am. Chem. Soc.* **1993**, *115*, 5941. Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellestad, K. E.; Stallman, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 7023. Nylund, C. S; Klopp, J. M.; Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 4287. Toyota, M.; Wada, T.; Nishikawa, Y.; Yanai, K.; Fukumoto, K. *Synlett* **1994**, 597. Toyota, M.; Nishikawa, Y.; Fukumoto, K. *Tetrahedron Lett.* **1994**, *35*, 6495.

(21) Nelson, R. P.; McEuen, J. M.; Lawton, R. G. *J. Org. Chem.* **1969**, *34*, 1225. Butkus, E; Bielinyte, B. *Prakt. J. Chem., Chem.-Ztg.* **1992**, *334*, 285.

(22) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. Lapierre, J. M.; Gravel, D. *Tetrahedron Lett.* **1991**, *32*, 2319.

(23) For transformations leading to synthetically useful intermediates, see *inter alia*: Eguchi, S.; Furukawa, Y.; Suzuki, T.; Kondo, K.; Sasaki, T.; Honda, M.; Katayama, C.; Tanaka, J. *J. Org. Chem.* **1985**, *50*, 1895. Suemune, H.; T.; Oda, K.; Sakai, K. *Tetrahedron Lett.* **1987**, *28*, 3373. Muir, D. J.; Stothers, J. B. *Can. J. Chem.* **1993**, *71*, 1290. Kelly, D. P.; Aherne, K.; Delgado, F.; Giansiracusa, J. J.; Jensen, W. A.; Karavokiros, K.; Mantello, R. A.; Reum, M. E. *J. Am. Chem. Soc.* **1993**, *115*, 12010. Engler, T. A.; Draney, B. W.; Gfesser, G. A. *Tetrahedron Lett.* **1994**, *35*, 1661. Chang, C. P.; Hsu, L. F.; Chang, N. C. *J. Org. Chem.* **1994**, *59*, 1898. Hayashi, Y.; Ushio, H.; Narasaka, K. *Chem. Lett.* **1994**, 289. Patel, H. A.; Stothers, J. B.; Thomas, S. E. *Can. J. Chem.* **1994**, *72*, 56.

(24) (a) Dauben, W. G.; MacFarland, J. W. *J. Am. Chem. Soc.* **1960**, *82*, 4245. (b) Grob, A.; Hostynek, J. *Helv. Chim. Acta* **1963**, *46*, 2209. (c) Buchanan, G. L.; Maxwell, C.; Henderson, W. *Tetrahedron* **1965**, *21*, 3273. (d) Buchanan, G. L.; McLay, G. W. *Tetrahedron* **1966**, *22*, 1521. (e) Buchanan, G. L.; Young, G. A. R. *J. Chem. Soc., Chem. Commun.* **1971**, 643. (f) Chakraborty, R.; Basu, M. K.; Ranu, B. C. *Tetrahedron* **1992**, *48*, 8849.

(25) Stork, G.; Landesman, H. K. *J. Am. Chem. Soc.* **1956**, *78*, 5129. Hendrickson, J. B.; Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 1307.

(26) Tanaka, M.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1988**, *29*, 1733.

(27) Schick, H.; Roatsch, B.; Schwarz, H.; Hauser, A.; Schwarz, S. *Liebigs Ann. Chem.* **1992**, 419.

(28) Maki, S.; Asaba, N.; Kosemura, S; Yamamura, S. *Tetrahedron Lett.* **1992**, *33*, 4169.

(29) Filippini, M. H.; Rodriguez, J. Santelli, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1647.

(30) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612. Crispin, D. J.; Vanstone, A. E.; Whitehurst, J. S. *J. Chem. Soc. (C)* **1970**, 10.

(31) Liu, H. J.; Ho, L. K.; Lai, H. K. *Can. J. Chem.* **1981**, *59*, 1685.

(32) Veselovskii, V.; Zhuzbaev, B. T.; Turdybekov, K. M.; Adekenov, S. M.; Struchkov, Yu. T.; Moiseenkov, A. M. *Izv. Akad. Nauk. Ser. Khim.* **1993**, *1*, 118.

(33) For preliminary results, see: Ouvrard, N.; Ouvrard, P.; Rodriguez, J.; Santelli, M. *J. Chem. Soc., Chem. Commun.* **1993**, 571.

controlling the Michael addition.[35] K_2CO_3 in acetone[36] (Table 1, condition A) was generally found to be a sufficiently strong base for condensations involving reactive aldehydes with β-keto esters **1a–e** (entries 1–17) or 2-acetylcyclopentanone (**1f**) (entries 18–20). In contrast, less satisfactory yields were obtained with Cs_2CO_3 (condition B) and no reaction took place with magnesium, sodium, and lithium carbonate or pyridine. However, DBU in acetone or in toluene (conditions C, D) proved to be a superior base in the case of less reactive aldehydes such as **2c**, **2f**, and **2g**, allowing stereoselective access to highly functionalized hydroxybicyclo[3.2.1]octanones such as **6**, **15**, and **16** (entries 8, 9, 23, 25). Up to five stereogenic centers are formed in this transformation. Pure ketols **3–16** are obtained in 30–99% yield as a generally separable mixture of isomers in which the one bearing an equatorial hydroxy group predominates in a ratio not exceeding 4/1.

Based on our previous results,[37] with prostereogenic aldehydes **2b,e–j** (Tables 1 and 2) the configuration at the newly created asymmetric centers is determined by the stereoselectivity of the kinetically controlled Michael addition, which is the first step of the condensative cyclization. Under the standard conditions reported in Table 1, the diastereomeric ratio varies from as little as 75:25 (entry 16) up to >97:3 (entry 14). Regardless of the reaction conditions, the condensation of 2-butenal (**2b**) with **1a** or **1f** proceeds with good selectivity in favor of the corresponding 4-axial-methyl substituted bicyclic compounds **7a** and **14a** (entries 10–12, 19). The minor diastereomers **7b** and **14b** are easily detected in the crude reaction mixture by ^1H NMR through the presence of the characteristic α-OH hydrogen pattern, which reveals the presence of a single isomer having the hydroxyl in the equatorial position. Moreover, **7b** was isolated and fully characterized by spectroscopic analysis and chemical transformations (*vide infra*). On the other hand, chiral (2*S*,3*R*)-β-keto esters **1c–e**[38] react smoothly with **2b** under condition A to provide, with high selectivity and in synthetically useful yields, **8a**, **9a**, and **10a**, respectively (entries 13–15). The highest diastereoselectivity is obtained with *tert*-butyl and benzyl esters **1d** and **1e**; no detection of the minor diastereomer **9b** and only traces of **10b** could be found in the crude product by ^1H NMR. In contrast, **8b** arising from methyl ester **1c** could be isolated by flash chromatography and fully characterized (*vide infra*). 2-Methylpropenal (**2d**) condenses with **1a** in acetone in the presence of K_2CO_3 to give, in good yield, **11** as a mixture of four diastereomers with a modest selectivity in favor of **11a** (entry 16). In contrast, 2-methyl-2-pentenal (**2f**) requires the use of DBU in toluene to reach an acceptable yield of **15**, obtained as a mixture of four diastereomers in which **15a** prevails (entries 21–23). Interestingly, with 1-formylcyclohexene (**2g**)[39] the *cis*-fused tricyclic equatorial alcohol **16a** is the only detectable isomer in the crude reaction mixture and could be isolated in 30% yield (entry 25). The result obtained with *trans*-2-hexenal (**2e**) clearly establishes the predominance of the steric factors on the stereochemical outcome of the condensation. Actually, compared to the high C-4-axial diastereoselectivity obtained with **2b** (>86%, entries 10–15, 19), the reaction of **2e** with **1a** is less selective and gives a 78:22 mixture of C-4-epimers **12a/b** (entry 17). Moreover, a comparable loss of the C-4-axial diastereoselectivity is observed with **2f** (entry 23). Further experimental evidence is provided by the reaction of bulky α,β-unsaturated aldehydes **2h–j** with **1a** (Table 2). Interestingly, the C-4 diastereoselectivity is reversed and the C-4-equatorial substituted bicyclic derivatives **17–19** are selectively obtained using K_2CO_3 in acetone. This can be rationalized if we consider that the gauche steric hindrance developed by the C-3 substituent of the Michael acceptor prevails over the repulsive nonbonding interaction responsible for the high C-4 axial diastereoselectivity observed with 2-butenal (**2b**).[37]

Structural Assignment. The structures of compounds **3–19** rest upon extensive ^1H and ^{13}C NMR studies. The well known γ-effect[40] in ^{13}C NMR, used initially in the structure assignment, proved to be consistent over the whole set of 41 bicyclic compounds prepared in this work (see Experimental Section). Moreover, chemical transformations confirmed these structures (*vide infra*). The following general trends can be observed: in the ^1H NMR spectra the signal due to the α-OH hydrogen appeared between δ 4.0–4.2 for the major equatorial-OH isomers and between δ 4.2–4.3 for axial derivatives, both presenting characteristic coupling constant patterns. On the other hand, besides a deshielding of the *C*HOH in all axial-OH isomers as compared to the equatorial-OH derivatives, ^{13}C NMR spectra show a large γ-effect at C-6 and C-7 (from 3.5 to 8.5 ppm), respectively, due to the presence of an equatorial-C-4 substituent and an equatorial-C-2-OH function. For example, equatorial-OH-**8a**, which serves as a model compound, reveals signals at δ 4.20 (ddd, J = 11.0, 5.8, 3.2 Hz) and 2.60 (broad dd, J = 7.4, 3.2 Hz) for *H*-C-2 and *H*-C-1, respectively (Figure 1).

The observed coupling constants clearly indicate an equatorially oriented hydroxyl group since the value found for $^3J_{H2-H3\alpha}$ = 11 Hz is in agreement with a 1,2-*trans*-diaxial arrangement.[41] Moreover, a ^1H-homonuclear two-dimensional chemical shift correlation experiment shows a cross-peak between the methyl substituent at C-4 and the axial *H*α-C-3 proton, characteristic of a *trans*-diaxial disposition.[42] Since the (*R*)-configuration at C-6 was given by the starting β-keto ester, we were able to corroborate the proposed stereochemistry for equatorial-OH-**8a**. The structure of axial-OH-**8a** was similarly deduced (Figure 1). The signal due to *H*-C-2 at δ = 4.31 (tdd, J = 4.5, 1.8, 1.2 Hz) shows two equatorial–equatorial ($^3J_{H1-H2}$ and $^3J_{H2-H3\beta}$), one equatorial–axial ($^3J_{H2-H3\alpha}$) and one $^4J_{H2-H4}$ coupling constant, which are in agreement with the *OH*-C-2 and the *Me*-C-4 in 1,3-*cis*-diaxial relation. Moreover, comparison of

(34) For recent successful base promoted condensative cyclizations leading to the parent bicyclo[3.3.1]nonane skeleton, see: Qian, L.; Ji, R. *Tetrahedron Lett.* **1989**, *30*, 2089. Kozikowski, A. P.; Xia, Y.; Reddy, E. R.; Tückmantel, W.; Hanin, I.; Tang, X. C. *J. Org. Chem.* **1991**, *56*, 4636. Gravel, D.; Benoît, S.; Kumanovic, S.; Sivaramakrishnan, H. *Tetrahedron Lett.* **1992**, *33*, 1403.

(35) Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1088.

(36) Barco, A.; Benetti, S.; Pollini, G. P. *Synthesis* **1973**, 316.

(37) Ouvrard, N.; Rodriguez, J.; Santelli, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1651.

(38) For the preparation of **1c** from (*R*)-(+)-pulegone, see: Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602. Compounds **1d,e** were prepared by esterification of pulegenic acid following the literature procedure: Murphy, C. F.; Koehler, R. E. *J. Org. Chem.* **1970**, *35*, 2429.

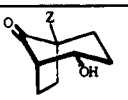
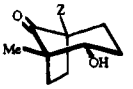
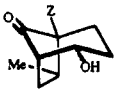
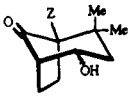
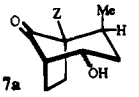
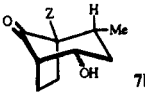
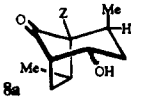
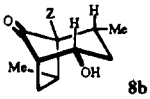
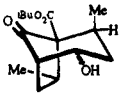
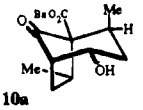
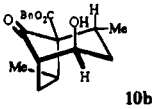
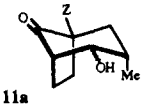
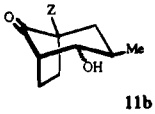
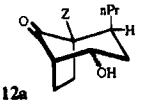
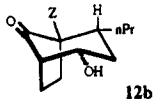
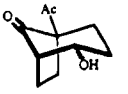
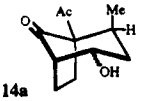
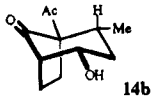
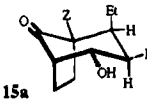
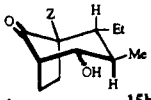
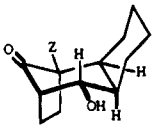
(39) Heilbron, I.; Jones, E. R. H.; Richardson, R. W.; Sondheimer, F. *J. Chem. Soc.* **1949**, 737.

(40) Grant, D. M.; Cheney, V. B. *J. Am. Chem. Soc.* **1967**, *89*, 5315.

(41) Günther, H. in *NMR Spectroscopy, an Introduction*; Wiley and Sons: New York, 1980.

(42) Platzer, N.; Goasdoue, N.; Davoust, D. *Magn. Reson. Chem.* **1987**, *25*, 311.

Table 1. Synthesis of 2-Hydroxybicyclo[3.2.1]octanones 3–16

Entry	1	2	Conditions [a]	Products (Z = COOMe)	Ratio [b] OH_{eq}/OH_{ax}	Diastereoselectivity [c] %	Yield [d] %
1	a	a	A, 15h	 **3a**	1.6	-	96
2			B, 3h 30		1	-	75
3			C, 3h 30		1	-	72
4	b	a	A, 18h	 **4a**	1.2	-	45
5	c	a	A, 20h	 **5a**	1.8	-	88
6	a	c	A, 96h		1.2	-	25
7			B, 72h	 **6a**	-	-	0
8			C, 96h[e]		n.d.[f]	-	58
9			D, 30h		1.3	-	87
10	a	b	A, 24h	 **7a** +  **7b**	3.8	88	90
11			B, 20h		3.6	88	52
12			D, 4h 30		3.4	86	51
13	c	b	A, 48h	 **8a** +  **8b**	2.7	85	72
14	d	b	A, 96h	 **9a**	2.8	> 97	65
15	e	b	A, 64h	 **10a** +  **10b**	2.8	> 95	61
16	a	d	A, 24h	 **11a** +  **11b**	2.8	75	78
17	a	h	A, 32h	 **12a** +  **12b**	3.7	78	99
18	f	a	A, 18h	 **13a**	1.5	-	64
19	f	b	A, 24h	 **14a** +  **14b**	2.5	90	68
20			D, 5h		n. d.[f]	n. d.[f]	30
21	a	f	A, 48h	 **15a** +  **15b**	-	-	0
22			C, 48h		-	-	21
23			D, 29h		n. d.[f]	78	65
24	a	g	A, 24h	 **16a**	-	-	0
25			D, 22h		-	>95	30

[a] A: K_2CO_3, acetone, RT; B: Cs_2CO_3, acetone, RT; C: DBU, acetone, RT; D: DBU, toluene, RT. [b] Determined by ^1H NMR spectroscopy (200 or 400 MHz). [c] Referred to the percentage of the major diastereomer (**a**), i. e. D = [**a**/**a**+**b**] 100% and determined by ^1H NMR spectroscopy (200 or 400 MHz). [d] Isolated. [e] Reflux. [f] n. d. : not determined.

Table 2. Reaction of 2h–j with 1a under Conditions A

2	Time (h)	Products (Z = COOMe)		Ratio [a] OH_{eq}/OH_{ax}	D (%)[b]	Yield[c] (%)
h	24	R = Ph	**17a**	**17b**	3.3	89	75
i	45	R = *o*-Anisyl	**18a**	**18b**	2.4	82	76
j	29	R = Furyl	**19a**	**19b**	1.6	72	78

[a] Determined by ^1H and ^{13}C NMR spectroscopies (200 or 400 MHz). [b] Referred to the percentage of the major diastereomer (**b**), i. e. D = [b/a+b] 100% determined by ^{13}C NMR spectroscopy (inverse gated decoupling, 200 and 400 MHz). [c] Isolated.

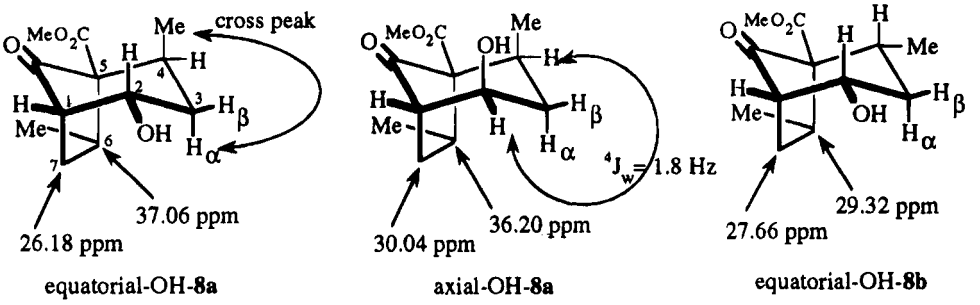
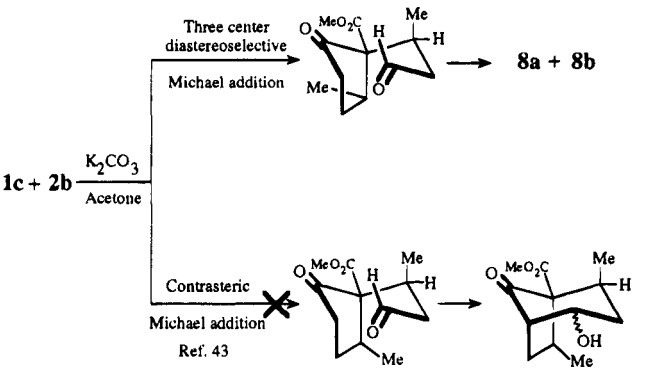


Figure 1. ^1H and ^{13}C NMR observations for **8a** and **8b**.

the ^{13}C NMR spectrum of equatorial- and axial-OH **8a** shows the disappearance of a γ-effect of about 4 ppm at C-7 due to the equatorial-OH.

The minor diastereomer **8b** was characterized using similar arguments. Only one hydroxy epimer could be isolated and presents the characteristic α-OH hydrogen *H*-C-2 at δ = 4.02 as a ddd with $^3J_{H2-H3\alpha}$ = 9.6 Hz indicating a *trans*-diaxial disposition with *H*α-C-3. On the other hand, the equatorial methyl at C-4 produces a γ-effect at C-6 of 7.7 ppm compared to equatorial-**8a** (Figure 1). This analysis established the proposed stereochemistry, which results from the highly diastereoselective three-center Michael addition.[37] A contrasteric Michael addition[43] leading to **20** can thus be rejected (Scheme 1).

Scheme 1



Control of the Diastereoselectivity. As expected from a recent study of the diastereoselectivity of the Michael addition,[37] it was found that the stereoselectivity of our condensative carbocyclization could be influenced by a simple modification of the reaction conditions (Table 3). For example, condensation of **1a** with **2b** in MeOH instead of acetone proceeds with very low diastereoselectivity in favor of **7a** when K_2CO_3 is used as base (entries 1, 2). From this result it seems that the base plays a minor role compared to the solvent system. Thus, using either DBU, DABCO, DMAP, or Et_3N in MeOH (entries 3–6) results in the more or less highly selective formation of **7b** while **7a** is the major isomer with DBU in acetone (entry 7) or toluene (entry 8). Increasing the polarity of the medium has a dramatic effect on the diastereoselectivity as shown by the addition of HMPA resulting in the selective obtention of **7b** (compare entries 8 and 9). Finally, a specific complexing agent combined with a high polarity medium has an even greater effect on the diastereoselectivity. Indeed, the complexation of the metal ion by Kryptofix 222[44] results in a reverse diastereoselectivity and **7b** is obtained with high selectivity (entry 10).[45]

Reactivity of Bicyclo[3.2.1]octane Derivatives. With an efficient stereoselective preparation of hydroxybicyclo[3.2.1]octanones in hand, we turned our attention to the reactivity of these derivatives, which constitute potential precursors of functionalized cycloheptanes.

(43) For a model for the diastereofacial differentiation in the alkylation of related endocyclic enolates with an asymmetric center at the β-position, see: Tomioka, K.; Kawasaki, H.; Yasuda, K.; Koga, K. *J. Am. Chem. Soc.* **1988**, *110*, 3597.

(44) Dietrich, B.; Lehn, J. M.; Sauvage, J. P. *Tetrahedron* **1973**, *29*, 1647.

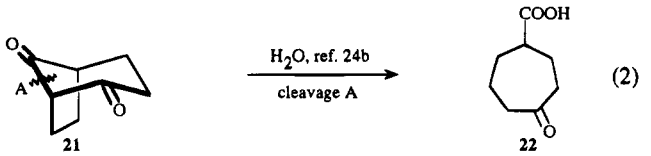
(45) For similar effects on the diastereoselectivity, see ref 37 and refs cited therein. Moreover, we found a similar observation during the reaction of cinnamaldehyde **2h** with **1a**, which gave the axial C-4 isomer **17a** (see Experimental Section) with high diastereoselectivity.

Table 3. Influence of the Reaction Conditions in the Condensation of 1a with 2b on the 7a:7b Ratio

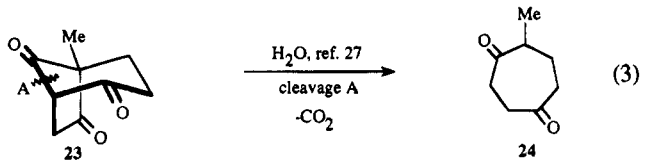
entry	conditions	7a:7b[a]
1	K_2CO_3, acetone, 15 h, rt	88:12
2	K_2CO_3, MeOH, 4 h, 0 °C	57:43
3	DBU, MeOH, 4 h, 0 °C	40:60
4	DABCO, MeOH, 23 h, rt	44:56
5	DMAP, MeOH, 96 h, rt	40:60
6	Et_3N, MeOH, 24 h, rt	35:65
7	DBU, acetone, 2 h, rt	73:23
8	DBU, toluene, 2 h, rt	86:14
9	DBU, toluene/HMPA (1/1), 20 h, rt	43:63
10	K_2CO_3, HMPA/CH_2Cl_2 (5/1), Kryptofix 222, cat., 8 h, −20 °C	>5:95

[a] Determined by ^1H NMR spectroscopy (200 or 400 MHz) on the crude reaction.

Previous reports on the reactivity of bicyclo[3.2.1]-octanediones prompted us to surmise that the oxidation of compounds **3**–**19** could provide access to substituted cycloheptanones. It is known that diketones **21**[24b] and triketones **23**[27] undergo hydrolytic ring opening (cleavage A) leading respectively to cycloheptanones **22** and **24** (eqs 2, 3).



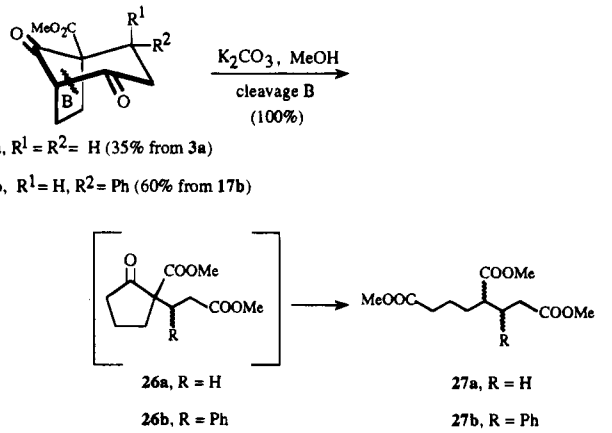
(2)



(3)

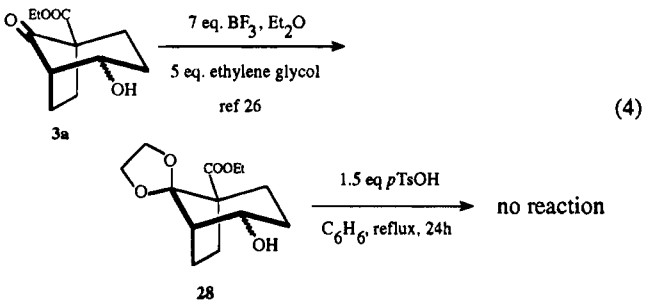
Unfortunately in our case diketones **25**, obtained by low temperature Jones oxidation[46] of the corresponding ketols, evolve upon treatment with K_2CO_3 in MeOH very rapidly and in quantitative yield to the open-chain triesters **27** (Scheme 2). The presence of the carbomethoxy substituent seems to be crucial in this transformation, which proceeds selectively by cleavage B,

Scheme 2



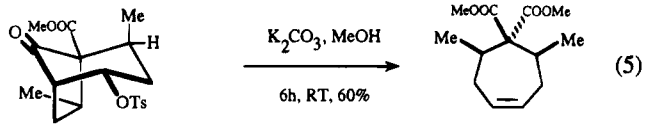
regardless of the substituent R^1 and R^2, to cyclopentanone intermediates **26**, precursors of **27** by a second retro-Dieckmann reaction.[47]

Application of the fragmentation of bicyclic acetal intermediates[26] also appeared ineffective with our substrates. Reaction of **3a** with ethylene glycol in the presence of an excess of $BF_3{\cdot}Et_2O$ gives only ethylene ketal **28**, which even proved to be stable over 24 h in the presence of 1.5 equiv of *p*-TsOH in refluxing benzene (eq 4).

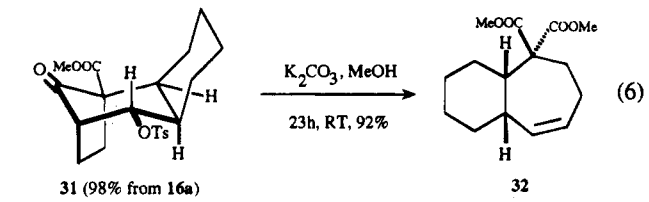


(4)

Another approach to the cycloheptane skeleton, based on the Grob type fragmentation[48] of tosylates, has been previously reported.[24c] As expected, equatorial-OTs **29** by a very clean fragmentation promoted by K_2CO_3 in MeOH gives *meso*-diester **30** in 60% yield (eq 5). Similarly, tricyclic derivative **31** is easily transformed into the functionalized *cis*-bicyclo[5.4.0]undecene **32**, with a ring system present in many naturally occurring compounds (eq 6).[49] Besides their synthetic potentialities these stereoselective transformations strongly support and confirm the proposed structure and stereochemistry of bicyclic ketols **8a** and **16a**.

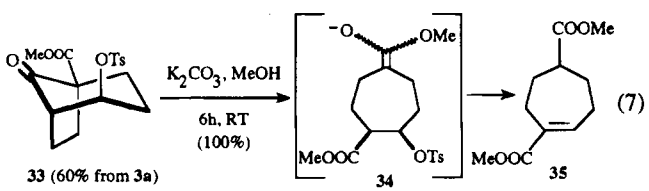


(5)



(6)

On the other hand, by analogy with previous results[24d] axial-OTs **33** treated under the same conditions gives the unstable cycloheptene **35** through a retro-Dieckmann reaction to **34** followed by a tosyl elimination (eq 7).

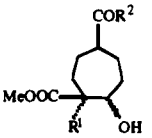
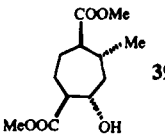
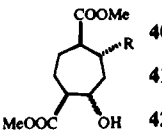
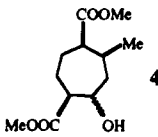


(7)

These results prompted us to study the behavior of the free bicyclooctanols under the base-promoted retro-Dieckmann ring cleavage conditions. We found that these substrates are effectively transformed to the ex-

(46) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.
(47) Filippini, M. H.; Rodriguez, J. *Synth. Commun.* **1995**, *25*, 245.
(48) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.
(49) Liu, H.-J.; Browne, N. C. *Can. J. Chem.* **1981**, *59*, 601.

Table 4. Retro-Dieckmann Ring Cleavage of Bicyclooctanols in MeOH

Compound	Conditions[a]	Product	Ratio[b] OH_{eq}/OH_{ax}	Yield (%)[c]
3a	A, 6h, 0°C	 **36**, R^1 = H, R^2 = OMe	1.5	96
4a	A, 16h, 20°C	**37**, R^1 = Me, R^2 = OMe	1.2	20
13a	A, 6h, 0°C	**38**, R^1 = H, R^2 = Me	1.4	70
7b	A, 6h, 20°C	 **39**	-	87
	B, 35h, 20°C		-	100
17b	A, 2h30, 20°C	 **40a,b**, R = Ph	2.8	60
18b	A, 2h30, 20°C	**41a,b**, R = *o*-Anisyl	1.3	67
19b	A, 2h30, 20°C	**42a,b**, R = Furyl	2.0	65
7a	A, 35h, 20°C		-	5[d]
	B, 35h, 20°C	**43** + **39**	-	13[d]
	B, 6h, 0°C		-	4[d]

[a] A: 1eq. K_2CO_3; B: 1eq. DBU. [b] Determined by ^1H NMR spectroscopy (200 or 400 MHz). [c] Isolated by FC on silica gel. [d] Yield of **39**.

pected cycloheptane derivatives by a clean reverse-Dieckmann reaction promoted by K_2CO_3 or DBU in MeOH (Table 4). For example, **3a**, **7b**, and **13a** react smoothly with K_2CO_3 or DBU in MeOH to give the corresponding functionalized cycloheptanols **36**, **38**, and **39** in very good yields, but **4a** furnishes **37** in only 20% isolated yield on treatment with K_2CO_3 in MeOH. The transformation of **17b**–**19b** requires DBU as base and cycloheptanols **40**–**42** are obtained as a separable mixture of hydroxy epimers. In sharp contrast, regardless of the reaction conditions, **7a** presenting an axial-Me substituent at C-4 failed to react cleanly either with K_2CO_3 or DBU giving exclusively polycondensation products. No evidence for the formation of the expected cycloheptanol **43** was found in the crude reaction mixture, but interestingly, **39** could be isolated in yields not exceeding 13%. This result, compared with the reactivity of **7b**, clearly establishes the influence of steric factors during the retro-Dieckmann ring cleavage.[47] It can be explained by invoking a tandem retro-aldol-retro-Michael ring opening of **7a** to give **1a** and **2b** followed by a thermodynamically controlled ring reconstitution leading to **7b**, precursor of **39**. The low yield observed in this transformation can be due to partial polymerization of **2b** and some degradation of **1a** by a retro-Dieckmann opening in the reaction conditions. Experimental evidence for this pathway was provided by a cross experiment in the presence of cinnamaldehyde (**2h**). Indeed, the reaction of a mixture of **7a** and **2h** with DBU in MeOH results in the formation of **39** (40%) and **40** (10%) accompanied by unreacted **7a** (50%).

Conclusion. The base-promoted tandem Michael addition–intramolecular aldol cyclization of α-carbonyl substituted cyclopentanones with α,β-unsaturated aldehydes proved to be a general stereoselective one-pot carbocyclization sequence. The stereoselectivity of this condensation can be partially controlled by simple experimental modifications. This allows the facile preparation of highly substituted, stereodefined, and optically active 2-hydroxybicyclo[3.2.1]octan-8-ones, precursors of functionalized cycloheptanes by a Grob-type fragmentation or by a mild retro-Dieckmann ring cleavage. Since the experimental conditions are extremely simple, inexpensive, and very mild, we hope that extensions of our methodology would be useful for the stereoselective preparation of complex natural and unnatural products.

Experimental Section

General. Melting points were observed in open Pyrex capillary tubes and are uncorrected. Optical rotations were recorded by using a 10 cm, 1 mL cell. FC (flash chromatography) was performed with Merck silica gel 60 (230–240 mesh).[50] TLC was performed on Alugram SIL G/UV 254 silica gel analytical plates with a 250 μm coating. Low and high resolution mass spectra were provided by the Mass Spectral Services at the University of Rennes I and elemental analyses were determined by the Microanalytical Services at the University of Marseille III.

Materials. Unless otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used without further purification. Commercial anhydrous analytical grade acetone (SDS) was used for the condensations while anhydrous MeOH, toluene, and THF were obtained, respectively, by distillation over magnesium and from sodium benzophenone under argon. Unless otherwise specified, all reactions involving air or moisture sensitive compounds were carried out under an atmosphere of dry argon.

General Procedures for the Preparation of 2-Hydroxybicyclo[3.2.1]octan-8-ones 3–19. Standard Conditions. To a solution of α-carbonyl substituted cyclopentanones **1** (1 mmol) in dry solvent (10 mL) was added the appropriate base (1.5 mmol), and the mixture was stirred under nitrogen for 15 min at room temperature. The α,β-unsaturated aldehyde **2** (1.5 mmol) in dry solvent (2 mL) was then slowly added

(50) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

via a syringe, and the evolution of the reaction was checked by TLC. After completion, when K_2CO_3 or Cs_2CO_3 were used, simple filtration through a short pad of Celite and evaporation of the filtrate under reduced pressure gave the crude bicyclic compounds, which were purified by FC. In the case of DBU or other soluble bases (DABCO, DMAP, Et_3N) the solvent and the volatiles were first eliminated under reduced pressure, the residue was dissolved in Et_2O (25 mL), acidified with 1 N HCl (15 mL), and the organic layer was extracted with Et_2O (3 × 25 mL), washed with H_2O (15 mL), and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude bicyclic compounds, which were purified by FC. **Inversion of the C-4 diastereoselectivity**: in this case, the reactions were performed at −20 °C following the general procedure. In the presence of Kriptofix 222[44] (0.25 equiv), K_2CO_3 was used as base and a mixture of HMPA/CH_2Cl_2 (5/1) as solvent. Under these conditions, bicyclic derivatives **7b** and **17b** were selectively obtained (Table 3).

Methyl *rac*-2-Hydroxy-8-oxobicyclo[3.2.1]octanecarboxylate (3a). Equatorial-OH epimer: mp 64–65 °C; IR ($CDCl_3$) 3480, 2945, 1755, 1720 cm^{-1}; ^1H NMR (200 MHz) δ 4.04 (dt, J = 3.4 and 5.6 Hz, 1 H), 3.71 (s, 3 H), 2.55 (m, 2 H), 1.96 (m, 2 H), 1.68 (m, 1 H); ^{13}C NMR (50 MHz) δ 221.24, 171.78, 73.43, 56.80, 54.12, 52.36, 31.12, 27.04, 26.27, 16.21. **Axial-OH epimer**: IR (neat) 3480, 2960, 1760, 1730 cm^{-1}; ^1H NMR (200 MHz) δ 4.28 (m, 1 H), 3.71 (s, 3 H), 2.54 (m, 2 H), 2.00 (m, 5 H), 1.69 (m, 2 H); ^{13}C NMR (50 MHz) δ 212.10, 171.78, 77.37, 57.38, 52.28, 52.14, 33.88, 25.79, 25.38, 19.29. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.57; H, 7.10.

Methyl *rac*-2-Hydroxy-1-methyl-8-oxobicyclo[3.2.1]-octanecarboxylate (4a). Two hydroxy isomers not separated: IR ($CDCl_3$) 3488, 2953, 1745, 1725 cm^{-1}. **Equatorial-OH epimer**: ^1H NMR (200 MHz) δ 3.92 (m, 1 H), 3.73 (s, 3 H), 3.70–3.56 (m, 2 H), 2.57–2.41 (m, 2 H), 2.20–1.60 (m, 5 H), 1.09 (s, 3 H); ^{13}C NMR (50 MHz) δ 210.92, 170.96, 74.18, 59.93, 55.38, 51.88, 35.97, 32.52, 27.24, 26.39, 21.05. **Axial-OH epimer**: ^1H NMR (200 MHz) characteristic signals δ 3.74 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (50 MHz) δ 211.64, 170.94, 77.99, 60.40, 53.39, 51.88, 35.67, 34.67, 30.35, 25.53, 21.11. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 60.27; H, 7.61.

Methyl (6*R*)-2-Hydroxy-6-methyl-8-oxobicyclo[3.2.1]-octanecarboxylate (5a). Two hydroxy isomers not separated: IR (neat) 3445, 2956, 1737, 1273 cm^{-1}. **Equatorial-OH epimer**: ^1H NMR (200 MHz) δ 4.09–4.05 (m, 1 H), 3.72 (s, 3 H), 2.62 (dd, J = 3.2 and 7.1 Hz, 1 H), 2.53–2.17 (m, 3 H), 2.06–1.93 (m, 1 H), 1.81–1.64 (m, 3 H), 1.43–1.33 (m, 1 H), 1.01 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (50 MHz) δ 210.92, 170.96, 74.18, 59.93, 53.38, 51.88, 35.97, 32.52, 27.24, 26.39, 21.05. **Axial-OH epimer**: ^1H NMR (200 MHz) characteristic signals δ 4.36–4.32 (m, 1 H), 3.73 (s, 3 H), 1.16 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 211.67, 170.96, 74.18, 59.93, 53.38, 51.88, 35.97, 32.52, 27.24, 26.39, 21.05. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 60.24; H, 7.57.

Methyl*rac*-2-Hydroxy-4,4-dimethyl-8-oxobicyclo[3.2.1]-octanecarboxylate (6a). Equatorial-OH epimer: IR (neat) 3450, 2970, 1755, 1735 cm^{-1}; ^1H NMR (200 MHz) δ 4.16 (td, J = 3.2 Hz and 8.2 Hz, 1 H), 3.68 (s, 3 H), 2.53 (m, 1 H), 2.00 (m, 3 H), 1.60 (d, J = 8.2 Hz, 2 H), 1.21 (m, 1 H), 1.11 (s, 3 H), 1.04 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (50 MHz) δ 209.69, 170.38, 69.21, 62.62, 53.36, 51.86, 42.85, 39.14, 25.47, 24.90, 24.36, 15.70. **Axial-OH epimer**: IR (neat) 3500, 2980, 1760, 1735 cm^{-1}; ^1H NMR (200 MHz) δ 4.21 (m, 1 H), 3.70 (s, 3 H), 2.46 (m, 1 H), 2.24 (m, 1 H), 1.85 (m, 3 H), 1.56 (m, 1 H), 1.35 (s, 3 H), 1.24 (m, 1 H), 1.06 (s, 3 H); ^{13}C NMR (50 MHz) δ 211.31, 170.23, 76.90, 63.19, 52.30, 51.27, 44.91, 41.03, 25.78, 25.43, 24.65, 19.51. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.71; H, 8.06.

Methyl *rac*-2-Hydroxy-4-(axial)-methyl-8-oxobicyclo-[3.2.1]octanecarboxylate (7a). Equatorial-OH epimer: mp 104–106 °C; IR (neat) 3500, 1760, 1730 cm^{-1}; ^1H NMR (400 MHz) δ 4.23 (dddd, J = 5.1, 5.1, 6.7 and 10.3 Hz, 1 H), 3.71 (s, 3 H), 2.56 (dd, J = 3.2 and 6.7 Hz, 1 H), 2.45 (dq, J = 5.9 and 6.9 Hz, 1 H), 2.31 (m, 1 H), 2.03 (ddd, J = 2.8, 10.9 and 21.8 Hz, 2 H), 1.83 (m, 3 H), 0.94 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 209.27, 171.98, 71.24, 59.44, 54.94, 52.10, 36.75, 33.79, 31.01, 16.90, 15.77. **Axial-OH epimer**: mp 95–97 °C; IR (neat) 3500, 2960, 1760, 1730 cm^{-1}; ^1H NMR (200 MHz) δ 4.20 (m, 1 H), 3.71 (s, 3 H), 2.68 (m, 1 H), 2.48 (m, 1 H), 2.20 (m, 1 H), 2.00 (m, 4 H), 1.63 (m, 1 H), 1.17 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (50 MHz) δ 210.95, 172.00, 79.75, 59.73, 53.46, 51.96, 43.28, 32.18, 30.30, 19.58, 18.00. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.20; H, 7.54.

Methyl *rac*-2-Hydroxy-4-(equatorial)-methyl-8-oxobicyclo[3.2.1]octanecarboxylate (7b): obtained diastereoselectively (>95/5) by addition of Kriptofix 222; IR (neat) 3500, 2955, 1755, 1730 cm^{-1}. **Equatorial-OH epimer**: ^1H NMR (200 MHz) δ 4.05 (dddd, J = 5.0, 5.0, 6.5 and 10.2 Hz, 1 H), 3.73 (s, 3 H), 2.56–2.30 (m, 3 H), 2.05–1.70 (m 1 H), 2.31 (m, 4 H), 2.03 (m, 1 H), 0.91 (d, J = 7.5, 3 H); ^{13}C NMR (50 MHz) δ 210.84, 170.38, 71.00, 61.45, 52.72, 51.92, 35.22, 35.22, 20.33, 15.94, 15.64. **Axial-OH epimer**: ^1H NMR (200 MHz) δ 4.20 (m, 1 H), 3.74 (s, 3 H), 0.88 (d, J = 6.5, 3 H); ^{13}C NMR (50 MHz) δ 211.57, 170.28, 75.34, 62.25, 52.10, 51.15, 37.77, 34.29, 19.58, 19.37, 16.34. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.26; H, 7.63.

Methyl (−)-(4*S*,6*R*)-2-Hydroxy-4,6-dimethyl-8-oxobicyclo[3.2.1]octanecarboxylate (8a). Equatorial-OH epimer: mp 102–104 °C; $[\alpha]^{26}_{578} = -47°$ (c = 2, $CHCl_3$); IR (neat) 3600, 2960, 1760, 1725 cm^{-1}; ^1H NMR (400 MHz) δ 4.20 (ddd, J = 3.2, 5.8 and 11.1 Hz, 1 H), 3.71 (s, 3 H), 2.60 (broad dd, J = 3.2 and 7.4 Hz, 1 H), 2.58 (dq, J = 1.5, 7.0 and 7.1 Hz, 1 H), 1.90 (ddd, J = 7.0, 11.1 and 14.0 Hz, 1 H), 1.77 (dddd, J = 1.1, 1.5, 5.8 and 14.0 Hz, 1 H), 1.29 (m, 1 H), 0.96 (d, J = 6.6, 3 H), 0.85 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz) δ 209.11, 170.66, 71.40, 63.99, 55.73, 51.66, 37.96, 37.06, 33.32, 26.18, 20.96, 17.17. **Axial-OH epimer**: mp 64–66 °C; $[\alpha]^{26}_{578} = -1.3°$ (c = 2, $CHCl_3$); IR (neat) 3600, 2965, 2940, 1770, 1725 cm^{-1}; ^1H NMR (400 MHz) δ 4.23 (dddd, J = 5.1, 5.1, 6.7 and 10.3 Hz, 1 H), 3.71 (s, 3 H), 2.56 (dd, J = 3.2 and 6.7 Hz, 1 H), 2.45 (dq, J = 5.9 and 6.9 Hz, 1 H), 2.31 (m, 1 H), 2.03 (ddd, J = 2.8, 10.9 and 21.8 Hz, 2 H), 1.83 (m, 3 H), 0.94 (d, J = 7.1, 3 H); ^{13}C NMR (100 MHz) δ 210.68, 170.66, 79.71, 64.41, 54.06, 51.58, 44.58, 36.20, 31.72, 30.04, 20.86, 18.48. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.67; H, 7.95.

Methyl (4*R*,6*R*)-2-(equatorial)-Hydroxy-4,6-dimethyl-8-oxobicyclo[3.2.1]octanecarboxylate (8b): IR (neat) 3500, 2940, 1760, 1740 cm^{-1}; ^1H NMR (200 MHz) δ 4.02 (ddd, J = 4.1, 5.5 and 9.6 Hz, 1 H), 3.71 (s, 3 H), 2.56 (m, 1 H), 2.36 (m, 1 H), 2.20 (m, 1 H), 1.80 (m, 2 H), 1.38 (m, 1 H), 1.16 (d, J = 6.6, 3 H), 1.00 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (50 MHz) δ 210.84, 170.15, 71.31, 64.30, 52.84, 51.60, 37.12, 35.79, 29.32, 27.66, 21.88, 16.63; MS m/e (relative intensity): $C_{12}H_{18}O_4$ M^+ 226 (18), 195 (19), 156 (62), 145 (34), 95 (55), 55 (63), 41 (70), 28 (88), 18 (100); HRMS: calcd 226.12050, obsd 226.1217.

***tert*-Butyl (−)-(4*S*,6*R*)-2-Hydroxy-4,6-dimethyl-8-oxobicyclo[3.2.1]octanecarboxylate (9a). Equatorial-OH epimer**: mp 133–135 °C; $[\alpha]^{26}_{578} = -50°$ (c = 1.5, $CHCl_3$); IR (neat) 3490, 2980, 1765, 1715 cm^{-1}; ^1H NMR (200 MHz) δ 4.17 (m, 1 H), 2.53 (m, 2 H), 2.32 (m, 2 H), 1.88 (m, 1 H), 1.78 (m, 1H), 1.44 (s, 9 H), 1.25 (m, 1 H), 1.02 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (50 MHz) δ 209.13, 168.89, 81.35, 71.53, 63.57, 55.69, 38.15, 36.74, 33.47, 28.10, 26.15, 21.09, 17.04. **Axial-OH epimer**: $[\alpha]^{26}_{578} = -2.6°$ (c = 1.5, $CHCl_3$); IR (neat) 3500, 2980, 2940, 1755, 1725 cm^{-1}; ^1H NMR (200 MHz) δ 4.23 (m, 1 H), 1.46 (s, 9 H), 1.18 (d, J = 7.1 Hz, 3 H), 1.03 (d, J = 5.5 Hz, 3 H); ^{13}C NMR (50 MHz) δ 207.16, 168.41, 81.27, 75.47, 64.80, 51.09, 39.44, 34.91, 29.70, 28.22, 28.13, 21.95, 16.67. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.19; H, 9.04.

Benzyl (−)-(4*S*,6*R*)-2-Hydroxy-4,6-dimethyl-8-oxobicyclo[3.2.1]octanecarboxylate (10a). Equatorial-OH epimer: $[\alpha]^{26}_{578} = -35°$ (c = 0.45, $CHCl_3$); IR (neat) 3480, 2960, 1755, 1730 cm^{-1}; ^1H NMR (200 MHz) δ 7.32 (m, 2 H), 5.14 (s, 2 H), 4.15 (m, 1 H), 2.75 (m, 1 H), 2.56 (m, 2 H), 2.36 (M, 2 H), 1.73 (m, 2 H), 1.26 (m, 1 H), 0.86 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 208.84, 169.76, 135.55, 128.51, 128.43, 128.65, 71.36, 66.33, 63.70, 55.65, 37.92, 36.94, 33.31, 26.16, 21.02, 17.11. **Axial-OH epimer**: $[\alpha]^{26}_{578} = -7°$ (c = 0.45, $CHCl_3$); ^1H NMR (200 MHz) δ 7.34 (m, 5 H), 5.16 (s, 2 H), 4.29 (m, 1 H), 2.80 (q, J = 7.0 Hz, 1 H),

2.22 (ddd, J = 4.4, 6.5 and 15.2 Hz, 1 H), 1.97 (dd, J = 9.5 Hz and 13.6 Hz, 1 H), 1.57 (d, J = 15.4 Hz, 1 H), 1.42 (ddd, J = 5.2, 7.3 and 13.1 Hz, 1 H), 1.07 (d, J = 7.2 Hz, 3 H), 0.90 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 209.95, 169.72, 135.75, 128.58, 128.44, 128.28, 79.85, 66.32, 64.21, 54.20, 44.58, 36.28, 31.94, 30.20, 18.55 (2 CH_3). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.53; H, 7.31.

Benzyl (4*R*,6*R*)-2-(axial)-Hydroxy-4,6-dimethyl-8-oxobicyclo[3.2.1]octanecarboxylate (10b). Equatorial-OH epimer: IR (neat) 3450, 2925, 1755, 1725 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.32 (m, 5 H), 5.17 (s, 2H), 4.15 (m, 1 H), 1.15 (d, J = 7.0 Hz, 3 H), 0.88 (d, J = 5.0 Hz, 3 H); ^{13}C NMR (50 MHz) δ 211.05, 169.11, 135.82, 128.25, 128.25, 128.05, 75.24, 66.33, 64.88, 50.72, 39.50, 34.54, 31.02, 27.92, 21.80, 16.58. Anal. Calcd for $C_{18}H_{22}O4$: C, 71.50; H, 7.33. Found: C, 71.55; H, 7.34.

Methyl *rac*-2-Hydroxy-3-(axial)-methyl-8-oxobicyclo-[3.2.1]octanecarboxylate (11a). Equatorial-OH epimer: IR ($CDCl_3$) 3500, 2965, 2930, 1755, 1730 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.73 (s, 3 H), 3.56 (dd, J = 3.6 and 8.4 Hz, 1 H), 2.55 (m, 1 H), 2.10–1.60 (m, 6 H), 1.10 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 210.66, 171.40, 78.81, 57.39, 53.37, 51.98, 39.91, 31.77, 27.22, 16.78, 16.54. **Axial-OH epimer**: mp 57 °C; ^{1}H NMR (200 MHz) δ 4.09 (m, 1 H), 3.72 (s, 3 H), 1.01 (d, J = 5.8 Hz, 3 H); ^{13}C NMR (50 MHz) δ 212.24, 171.56, 79.48, 56.55, 52.00, 51.83, 40.72, 28.76, 26.22, 18.71, 15.27. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.25; H, 7.63.

Methyl *rac*-2-Hydroxy-3-(equatorial)-methyl-8-oxobicyclo[3.2.1]octanecarboxylate (11b). Axial-OH epimer: IR ($CDCl_3$) 3500, 2970, 1760, 1730 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.00 (m, 1 H), 3.73 (s, 3 H), 2.87 (dq, J = 6.0 and 7.2 Hz, 1 H), 2.50 (m, 1 H), 2.30 (m, 2 H), 1.85 (m, 3 H), 1.60 (m, 1 H), 1.16 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (50 MHz) δ 212.08, 171.81, 85.00, 55.97, 52.24, 51.40, 40.74, 33.89, 29.30, 20.98, 19.27. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.25; H, 7.61.

Methyl *rac*-2-Hydroxy-4-(axial)-*n*-propyl-8-oxobicyclo-[3.2.1]octanecarboxylate (12a). Equatorial-OH epimer: IR (neat) 3485, 2955, 1756, 1726 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.17–4.12 (m, 1 H), 3.69 (s, 3 H), 2.56–2.52 (m, 1 H), 2.36–1.64 (m, 9 H), 1.42–1.11 (m, 3 H), 0.87–0.81 (m, 3 H); ^{13}C NMR (50 MHz) δ 209.31, 171.76, 70.77, 58.81, 54.38, 51.54, 41.30, 31.82, 30.40, 28.58, 20.93, 15.13, 13.32. **Axial-OH epimer**: ^{1}H NMR (400 MHz) δ 4.30 (s broad, 1H), 3.72 (s, 3 H), 2.52–2.40 (m, 2 H), 2.29–2.11 (m, 2 H), 2.05-1.87 (m, 2 H), 1.85–1.77 (m, 1 H), 1.67–1.48 (m, 2 H), 1.47–1.27 (m, 2 H), 1.26-1.09 (m, 2 H), 0.86–0.81 (m, 3 H); ^{13}C NMR (50 MHz) δ 211.44, 172.17, 79.78, 59.42, 53.41, 51.87, 48.30, 30.20, 32.35, 30.20, 26.88, 21.32, 19.41, 13.71. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.01; H, 8.35.

Methyl *rac*-2-Hydroxy-4-(equatorial)-*n*-propyl-8-oxobicyclo[3.2.1]octanecarboxylate (12b). Equatorial-OH epimer: IR (neat) 3471, 2956, 1764, 1732 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.02–3.98 (m, 1 H), 3.72 (s, 3 H), 2.49–2.42 (m, 1 H); ^{13}C NMR (50 MHz) δ 210.53, 170.25, 70.96, 61.47, 52.84, 51.88, 39.71, 33.10, 32.07, 20.56, 19.70, 15.55, 13.46. **Axial-OH epimer**: ^{1}H NMR (400 MHz) δ 4.23 (s broad, 1 H), 3.71 (s, 3 H), 2.80–2.73 (m, 1 H), ^{13}C NMR (50 MHz) δ 211.94, 170.59, 75.15, 62.39, 51.99, 51.27, 42.50, 33.84, 31.39, 21.32, 20.00, 19.72, 19.20, 13.91. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.92; H, 8.41.

***rac*-5-Acetyl-2-hydroxy-8-oxobicyclo[3.2.1]octane (13a).** Two isomers not separated: IR (neat) 3475, 2960, 1740, 1700 cm^{-1}. **Equatorial-OH epimer**: ^{1}H NMR (200 MHz) δ 4.12–4.05 (m, 1 H), 2.60–1.62 (m, 9 H), 2.15 (s, 3 H); ^{13}C NMR (50 MHz) δ 213.13, 207.11, 73.89, 62.02, 54.60, 31.03, 27.57, 26.52, 26.26, 16.21. **Axial-OH epimer**: ^{1}H NMR (200 MHz) characteristic signals δ 4.37–4.30 (m, 1 H), 2.21 (s, 3 H); ^{13}C NMR (50 MHz) δ 214.10, 207.23, 77.37, 62.31, 52.40, 33.81, 27.45, 25.23, 24.31, 18.94. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.90; H, 7.73.

***rac*-5-Acetyl-2-hydroxy-4-(axial)-methyl-8-oxobicyclo-[3.2.1]octane (14a). Equatorial-OH epimer**: IR (neat) 3470, 2970, 1735, 1680 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.30–4.20 (m, 1 H), 2.57–2.54 (m, 2H), 2.32–2.04 (m, 2 H), 2.19 (s, 3 H), 1.98-1.64 (m, 5 H), 0.81 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 212.52, 207.19, 71.49, 65.80, 55.07, 35.97, 33.54, 29.31, 28.10, 16.51, 16.00. **Axial-OH epimer**: IR (neat) 3470, 2970, 1735, 1690 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.40–4.30 (m, 1 H), 2.20 (s, 3H), 1.05 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (50 MHz) δ 214.36, 207.41, 79.82, 66.91, 53.39, 42.62, 32.03, 28.43, 28.15, 19.54, 16.40. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.30; H, 8.25.

***rac*-5-Acetyl-2-(equatorial)-hydroxy-4-(equatorial)-methyl-8-oxobicyclo[3.2.1]octane (14b).** Detected in the crude by the following characteristic signals: ^{1}H NMR (200 MHz) δ 4.11–4.06 (m, 1 H), 2.32 (s, 3 H), 0.86 (d, J = 7.3 Hz, 3 H).

Methyl *rac*-4-(axial)-Ethyl-2-(equatorial)-hydroxy-3-(equatorial)-methyl-8-oxobicyclo[3.2.1]octanecarboxylate (15a). Major isomer in the crude: IR (neat) 3478, 2967, 1730, 1268 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.72 (s, 3 H), 3.68 (dd, J = 10.3 and 3.6 Hz, 1 H), 2.51 (dd, J = 6.5 and 3.6 Hz, 1 H), 2.30–2.25 (m, 1 H), 2.08–1.95 (m, 4 H), 1.85–1.50 (m, 4 H), 1.12 (d, J = 6.4 Hz, 3 H), 0.96 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 209.33, 172.55, 76.23, 61.18, 54.22, 52.07, 48.46, 34.43, 30.43, 21.47, 16.21, 15.55, 13.78. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.00; H, 8.37.

Methyl *rac*-(2*S*,3*R*,8*S*)-2-hydroxy-12-oxotricyclo-[7.2.1.0^{3,8}]dodecanecarboxylate (16a): R_f 0.1 (ethyl ether/pentane, 9/1); IR (neat) 3479, 2934, 1732, 1269 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.09 (dd, J = 10.5 and 3.4 Hz, 1 H), 3.71 (s, 3 H), 2.54 (dd, J = 6.8 and 3.5 Hz, 1 H), 2.36–2.14 (m, 4 H), 2.08–1.94 (m, 4 H), 1.92–1.72 (m, 2 H), 1.60–1.50 (m, 2 H), 1.49–1.18 (m, 2 H); ^{13}C NMR (50 MHz) δ 209.21, 171.90, 70.68, 59.96, 54.15, 51.95, 44.13, 35.60, 30.39, 25.91, 24.99, 24.64, 20.62, 16.06. Anal. Calcd for $C_{14}H_{20}O_4$: C, 60.30; H, 7.53. Found: C, 60.28; H, 7.31.

Methyl *rac*-2-(equatorial)-Hydroxy-4-(axial)-phenyl-8-oxobicyclo[3.2.1]octanecarboxylate (17a). Obtained diastereoselectivly (>90/10) by addition of Kryptofix 222: ^{1}H NMR (200 MHz) δ 7.25–7.19 (m, 5 H), 4.24–4.10 (m, 1 H), 4.05 (dd, J = 10.9 and 3.6 Hz, 1 H), 3.55 (s, 3 H), 2.69 (dd, J = 6.4 Hz and 3.2 Hz, 1 H), 2.59–1.73 (m, 6 H); ^{13}C NMR (50 MHz) δ 209.44, 171.23, 141.69, 128.02, 127.73, 126.35, 70.77, 65.53, 54.21, 51.71, 49.18, 33.59, 31.57, 14.94.

Methyl *rac*-2-(axial)-Hydroxy-4-(equatorial)-phenyl-8-oxobicyclo[3.2.1]octanecarboxylate (17b): mp 46–48 °C; R_f 0.2 (ethyl ether/pentane, 9/1); IR (CCl_4) 3500, 3040, 2960, 1760, 1730, 1600 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.24–7.09 (m, 5 H), 4.28–4.20 (m, 1 H), 3.98 (dd, J = 4.8 Hz, 1 H), 3.55 (s, 3 H), 2.62–1.88 (m, 7 H), 1.87–1.69 (m, 1 H); ^{13}C NMR (50 MHz) δ 210.29, 169.58, 139.84, 128.11, 127.73, 126.35, 74.06, 62.15, 51.70, 51.24, 47.33, 32.90, 20.35, 19.02. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.07; H, 6.58.

Methyl *rac*-2-Hydroxy-4-(equatorial)-*o*-anisyl-8-oxobicyclo[3.2.1]octanecarboxylate (18b). Equatorial-OH epimer: ^{13}C NMR (50 MHz) δ 209.83, 170.57, 156.69, 129.09, 125.76, 127.54, 120.02, 110.67, 70.96, 60.69, 55.20, 54.01, 51.88, 39.00, 33.61, 23.14, 16.64. **Axial-OH epimer**: IR (neat) 3480, 2954, 1741, 1727, 1245, 912, 732 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.21–7.05 (m, 2 H), 6.85–6.82 (m, 2 H), 4.37 (dd, J = 13.1 and 4.4 Hz, 1 H), 4.30–4.20 (m, 1 H), 3.81 (s, 3 H), 3.52 (s, 3 H), 2.62 (dd, J = 8.3 and 5.5 Hz, 1 H), 2.55–2.25 (m, 3 H), 2.24–1.86 (m, 3 H), 1.73–1.61 (m, 1 H); ^{13}C NMR (50 MHz) δ 210.51, 170.50, 156.59, 129.66, 127.46, 125.92, 120.17, 110.72, 74.75, 61.26, 55.20, 52.22, 52.05, 40.95, 32.80, 21.83, 19.54. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.05; H, 6.62.

Methyl *rac*-2-(equatorial)-Hydroxy-4-(axial)-furyl-8-oxobicyclo[3.2.1]octanecarboxylate (19a): ^{13}C NMR (50 MHz) δ 209.35, 169.80, 152.74, 142.12, 110.24, 107.38, 70.91, 61.23, 53.34, 52.39, 40.29, 31.24, 30.82, 16.01.

Methyl *rac*-2-Hydroxy-4-(equatorial)-furyl-8-oxobicyclo-[3.2.1]octanecarboxylate (19b). Equatorial-OH epimer: IR ($CDCl_3$) 3486, 2956, 1729, 1277, 908 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.29–7.24 (m, 1 H), 6.27–6.19 (m, 1 H), 6.07–6.02 (m, 1 H), 4.47–4.39 (m, 1 H), 4.16 (dd, J = 12.2 and 5.3 Hz, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 2.68–1.69 (m, 5 H); ^{13}C NMR (50 MHz) δ 207.51, 171.35, 153.59, 141.36, 110.24, 107.02,

71.29, 57.34, 54.53, 52.99, 41.76, 31.65, 21.87, 15.64. **Axial-OH epimer**: ^{1}H NMR (200 MHz) δ characteristic signals 4.38–4.25 (m, 1 H);^{13}C NMR (50 MHz) δ 209.98, 169.80, 152.74, 142.12, 110.24, 107.38, 74.38, 61.78, 52.33, 51.40, 42.20, 30.85, 20.85, 19.29. Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.60; H, 6.11.

Preparation and Cleavage of Bicyclo[3.2.1]octanedione 25. Bicyclic diketones **25a,b** were obtained by low temperature (−30 °C) Jones oxidation[46] of the corresponding ketols **3a** and **17b**. **Cleavage**: To an ice cold solution of diketones **25** (1 mmol) in anhydrous MeOH (5 mL) was added K_2CO_3 (1 mmol), and the heterogeneous mixture was stirred under nitrogen at room temperature until no more starting material was visible on TLC. After completion, the mixture was then filtered through a short pad of Celite and the filtrate concentrated under reduced pressure to give the crude acyclic derivatives **27a,b**,[51] which were purified by flash chromatography on silica gel using Et_2O/pentane as eluant.

Methyl *rac*-2,8-Dioxobicyclo[3.2.1]octanecarboxylate (25a) (35% from **3a**): mp 80–82 °C; R_f 0.1 (ethyl ether/pentane, 1/1); IR (CCl_4) 2950, 1760, 1740, 1725 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.80 s, 3 H), 3.30 (d, J = 3.3 Hz, 1 H), 2.90–2.40 (m, 4 H), 2.40–1.90 (m, 4 H); ^{13}C NMR (50 MHz) δ 204.31, 202.11, 170.43, 64.30, 54.40, 52.46, 33.8, 27.38, 26.18, 21.58. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.22; H, 6.16.

Methyl *rac*-4-(equatorial)-Phenyl-2,8-dioxobicyclo-[3.2.1]octanecarboxylate (25b) (60% from **17b**): R_f 0.1 (ethyl ether/pentane, 1/1); IR (neat) 2959, 1726, 1776, 1275 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.20 (m, 4 H), 6.96 (dd, J= 3.6 and 7.7 Hz, 1 H), 3.76 (d, J = 9.2 Hz, 1 H), 3.63 (s, 3 H), 3.46 (d, J = 6.58 Hz, 1 H), 3.31 (dd, J = 9.1 and 16.8 Hz, 1 H), 2.67 (d, J = 17.0 Hz, 1 H), 2.57–2.15 (m, 4 H); ^{13}C NMR (50 MHz) δ 205.92, 199.82, 170.08, 139.50, 128.26, 128.11, 127.63, 65.76, 60.03, 52.15, 44.63, 41.20, 30.19, 21.65. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 60.28; H, 7.31.

Dimethyl 4-[(Methyloxy)carbonyl]-3-phenyloctanedioate (27b). Two isomers (1/1): IR (neat) 2956, 1735, 1438, 1260, 1156 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.27–7.20 (m, 5 H), 3.70/3.63/3.56/3.52/3.46/3.43 (s, 9 H), 3.40–3.25 (m, 1 H), 2.63–2.13 (m, 2 H), 2.20–2.13 (m, 2 H), 1.57–1.10 (m, 5 H); ^{13}C NMR (50 MHz) δ 175.21/174.27/173.55/172.34, 140.95, 128.66/128.36/127.92/127.16/127.09, 51.81/51.56, 51.05/44.40/43.98, 39.36/37.63/33.73/33.63/29.09/22.70/22.74. Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.22.

***rac*-2-Hydroxy-6-(ethoxycarbonyl)bicyclo[3.2.1]octan-8-one Ethylene Ketal (28).** Two isomers (1.5/1): R_f 0.26 (ethyl ether/pentane, 9/1); IR (neat) 3520, 2900, 1720, 1275 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.20–3.80 (m, 6 H), 2.55–1.50 (m, 10 H), 1.30–1.15 (m, 4 H); ^{13}C NMR (50 MHz) δ 173.69, 173.14, 116.56, 116.13, 73.40, 66.61, 64.17, 64.11, 66.08, 66.04, 65.72, 65.47, 60.29, 60.17, 51.99, 51.77, 46.84, 44.99, 29.92, 29.13, 26.14, 26.11, 25.77, 21.67, 17.73, 13.97; MS m/e (relative intensity): $C_{13}H_{20}O_5$ M^+ 256 (3), 238 (86), 211 (33), 128 (41), 99 (100), 55 (37), 28 (37); HRMS: calcd 256.13106, obsd 256.13230.

Preparation and Cleavage of Tosylates 29, 31, and 33. Tosylation of equatorial-ketones **8a** and **16a** and axial-ketol **3a** under standard conditions[52] gave the corresponding tosylates **29**, **31**, and **33** in 95, 98, and 60% yield, respectively, after FC on silica gel. **Cleavage.** Cycloheptenes **30**, **32**, and **35** were obtained by reaction of the corresponding tosylates **29**, **31**, and **33** following the procedure previously described for the ring cleavage of diketones **25** (vide supra).

Methyl (2*S*,4*S*,6*R*)-4,6-Dimethyl-2-*p*-tosyl-8-oxobicyclo-[3.2.1]octanecarboxylate (29): R_f 0.61 (ethyl ether/pentane, 1/1); IR (neat) 2960, 1760, 1730, 1600, 730 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.74 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.2 Hz, 2 H), 4.71–4.68 (m, 1 H), 3.69 (s, 3 H), 3.70 (s, 3 H), 2.65–2.20 (m, 6 H), 2.20–2.00 (m, 2 H), 1.90–1.75 (m, 1 H), 1.35–1.15 (m, 2 H), 0.92 (d, J = 5.9Hz, 3 H), 0.79 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz) δ 205.39, 169.46, 144.94, 133.44, 128.91, 127.31, 79.54, 63.66, 52.56, 51.45, 36.80, 36.28, 31.24, 26.28, 21.38, 20.52, 16.47. Anal. Calcd for $C_{19}H_{24}O_6S$: C, 59.98; H, 6.36; S, 8.43. Found: C, 59.94; H, 6.31; S, 8.40.

Dimethyl *cis*-4,6-dimethyl-1-cycloheptene-5,5-dicarboxylate (30) (60% from **29**): R_f 0.66 (ethyl ether/pentane, 1/1); IR (neat) 2980, 1730, 1250, 1200 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.60 (dd, J = 2.3 and 4.1 Hz, 2 H), 3.68 (s, 3 H), 3.65 (s, 3 H), 2.39–2.30 (ddd, J = 1.3, 10.3 and 15.3 Hz, 3 H), 2.30–2.10 (m, 2 H), 2.13–2.06 (dm, J = 15.3 Hz, 2 H), 1.05 (d, J = 6.9 Hz, 6 H); ^{13}C NMR (50 MHz) δ 173.09, 170.39, 129.61, 144.94, 66.57, 52.00, 51.28, 40.16, 33.75, 20.35. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.34. Found: C, 65.00; H, 8.31.

Methyl *rac*-(2*S*,3*R*,8*S*)-2-*p*-tosyl-12-oxotricyclo[7.2.1.0^{3,8}]-dodecanecarboxylate (31): R_f 0.60 (ethyl ether/pentane, 9/1); IR (neat) 2932, 1734, 1452, 1174 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.78 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 4.70 (dd, 3.8 and 10.3 Hz, 1 H), 3.69 (s, 3 H), 2.70 (dd, J = 3.4 and 6.6 Hz, 1 H), 2.43 (m, 3 H), 2.29–2.09 (m, 4 H), 2.04–1.94 (m, 2 H), 1.90–1.65 (m, 4 H), 1.23–1.11 (m, 4 H); ^{13}C NMR (50 MHz) δ 205.694, 171.20, 145.17, 133.46, 129.80, 127.87, 80.17, 59.71, 52.22, 51.25, 43.07, 34.21, 29.99, 25.60, 25.00, 24.45, 21.65, 20.21, 16.60. Anal. Calcd for $C_{21}H_{26}O_6S$: C, 62.05; H, 6.45, S, 7.89. Found: C, 61.99; H, 6.48; S, 7.80.

***rac*-Dimethyl *cis*-bicyclo[5.4.0]undecene-6,6-dicarboxylate (32)** (92% from **31**): R_f 0.60 (ethyl ether/pentane, 9/1); IR (neat) 2932, 1729, 1638, 910, 736 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.82–5.75 (m, 1 H), 5.37–5.31 (m, 1 H), 3.70 (s, 3 H), 3.66 (s, 3 H), 3.16 (s broad, 1 H), 2.45–2.08 (m, 4 H), 1.95–1.19 (m, 14 H), 0.96–0.89 (m, 1 H); ^{13}C NMR (50 MHz) δ 172.10, 171.85, 135.14, 130.29, 63.20, 52.59, 52.40, 43.25, 35.25, 34.00, 27.39, 26.70, 24.37, 24.05, 21.42. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.64; H, 8.31.

Methyl *rac*-2(*R*)-*p*-tosyl-8-oxobicyclo[3.2.1]octanecarboxylate (33): mp 95–97 °C; IR (neat) 2960, 1760, 1730 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.85 (d, J = 9.0 Hz, 2 H), 7.77 (d, J = 9.0 Hz, 2 H), 3.72 (s, 3 H), 2.74–2.43 (m, 4 H), 1.97–1.95 (m, 2 H), 1.54 (s, 3 H), 1.31–1.23 (m, 3 H). Anal. Calcd for $C_{17}H_{20}O_6S$: C, 57.94; H, 5.72; S, 9.10. Found: C, 57.95; H, 5.72; S, 9.12.

***rac*-1,5-Bis[(methyloxy)carbonyl]-1-cycloheptene (35)** (100% from **33**): IR (neat) 3160, 2940, 1710, 1660 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.10 (m, 1 H), 3.68 (s, 3 H), 3.62 (s, 3 H), 2.81–2.77 (m, 1 H), 2.65–2.21 (m, 3 H), 2.04–1.54 (m, 5 H); ^{13}C NMR (50 MHz) δ 180.73, 166.35, 143.53, 135.66, 53.45, 52.08, 46.67, 33.68, 27.74, 27.36, 26.40. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.20; H, 7.62.

General Procedure for the Preparation of Cycloheptanols 36–42 (see Table 4). To an ice cold solution of the corresponding ketols (1 mmol) in anhydrous MeOH (5 mL) was added the appropriate base (1 mmol), and the mixture was stirred under argon at the selected temperature until completion of the reaction (TLC). Depending on the nature of the base, a simple filtration (K_2CO_3) followed by concentration under reduced pressure, or a standard workup (DBU), gave the crude cycloheptanols **36–42**, which were purified by FC on Et_3N deactivated silica gel.

***rac*-(2*S*,5*R*)-Bis[(methyloxy)carbonyl]cycloheptan-1-ol (36).** Two hydroxy epimers not separated: R_f 0.40 (ethyl ether/pentane, 7/3); IR (neat) 3500, 2950, 2890, 1730 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.95 (m, 1 H), 3.75 (s, 3 H), 3.65 (s, 3 H), 3.35, (m, 1 H), 2.80–2.20 (m, 2 H), 2.20–1.52 (m, 8 H); ^{13}C NMR (50 MHz) δ 176.61, 176.23, 175.77, 175.63, 73.52, 69.39, 53.16, 50.61, 51.68, 51.65, 51.51, 51.46, 44.29, 43.16, 33.72, 31.34, 29.19, 27.45, 24.98, 23.88, 24.02, 22.91. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.41; H, 7.88.

***rac*-(2*S*,5*R*)-2,5-Bis[(methyloxy)carbonyl]-2-methylcycloheptan-1-ol (37).** Two hydroxy epimers not separated: IR (neat) 3445, 2930, 1735, 1457, 1260 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.90–4.08 (m, 1 H), 3.70 (s, 3 H), 3.63 (s, 3 H), 2.48–1.63 (m, 6 H), 1.47–1.18 (m, 4H), 1.16 (s, 3 H); ^{13}C NMR (50 MHz) δ 178.83, 176.50, 75.59, 52.34, 51.78, 50.00, 45.99, 33.46, 30.40, 28.25, 25.02, 11.10. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.02; H, 8.20.

***rac*-(2*S*,5*R*)-5-Acetyl-2-[(methyloxy)carbonyl]cycloheptan-1-ol (38).** Two hydroxy epimers not separated: R_f 0.26 (ethyl ether/pentane, 9/1); IR (neat) 3450, 2940, 2880, 1740, 1720 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.05–3.80 (m, 1 H), 3.70 (s,

(51) Compound **27a** has been previously described in ref 47.
(52) Kabalka, G. W.; Varma, R. S. *J. Org. Chem.* **1986**, *51*, 2386.

3 H), 2.65–1.40 (m, 11 H), 1.30–1.15 (m, 3 H); ^{13}C NMR (50 MHz) δ 211.22, 175.93, 73.87, 72.84, 54.07, 52.20, 46.13, 32.57, 34.03, 28.45, 28.22, 26.57, 25.77, 24.28, 24.11, 23.14. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.68; H, 8.53.

***rac*-(1*S*,2*S*,5*R*,6*R*)-2,5-Bis[(methyloxy)carbonyl]-6-methylcycloheptan-1-ol (39)**: mp 60–62 °C; R_f 0.21 (ethyl ether/pentane, 9/1); IR (neat) 3540, 2960, 2880, 1735 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.94 (td, J = 9.8 and 2.5 Hz, 1 H), 3.63 (s, 3 H), 3.58 (s, 3 H), 2.32 (ddd, J = 9.8, 8.2 and 4.8 Hz, 1 H), 2.09 (dt, J = 10.4 and 5.3 Hz, 1 H), 1.98 (m, 1 H), 1.86–1.67 (m, 4 H), 1.67–1.56 (m, 2 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz) δ 176.51, 175.92, 73.01, 53.72, 51.76, 51.93, 51.63, 42.21, 31.95, 27.87, 23.94, 22.74. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.00; H, 8.20.

***rac*-(1*S*,2*S*,5*R*,6*R*)-2,5-Bis[(methyloxy)carbonyl]-6-phenylcycloheptan-1-ol (40a)**: R_f 0.37 (ethyl ether/pentane, 9/1); IR (neat) 3443, 2946, 1731, 1443, 1163, 917, 734, 702 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.29–7.10 (m, 5 H), 4.16 (dt, J = 2.8 and 10 Hz, 1 H), 3.73 (s, 3 H), 3.43 (s, 3 H), 3.17 (dt, J = 1.7 and 10.8 Hz, 1 H), 2.75–2.60 (m, 1 H), 2.58–2.47 (m, 1 H), 1.13–0.95 (m, 7 H); ^{13}C NMR (50 MHz) δ 175.75, 175.61, 145.60, 128.54, 126.96, 126.52, 73.32, 53.70, 52.06, 51.52, 51.87, 43.48, 41.66, 27.97, 23.90. Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.68; H, 7.25.

***rac*-(1*R*,2*S*,5*R*,6*R*)-2,5-Bis[(methyloxy)carbonyl]-6-phenylcycloheptan-1-ol (40b)**: R_f 0.46 (ethyl ether/pentane, 9/1); IR (neat) 3508, 2949, 1729, 1441, 1199, 733, 702 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.28–7.17 (m, 5 H), 4.45 (broad d, J = 7 Hz, 1 H), 3.75 (s, 3 H), 3.29 (s, 3 H), 3.12–3.11 (m, 2 H), 2.64–2.58 (m, 2 H), 2.45–2.16 (m, 3 H), 2.03–1.86 (m, 3 H); ^{13}C NMR (50 MHz) δ 176.38, 176.61, 144.52, 128.18, 127.87, 126.37, 68.08, 52.15, 52.03, 51.05, 49.53, 38.64, 38.85, 27.92, 23.72. Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.68; H, 7.25.

***rac*-(1*S*,2*S*,5*R*,6*R*)-2,5-Bis[(methyloxy)carbonyl]-6-*o*-anisylcycloheptan-1-ol (41a)**: R_f 0.14 (ethyl ether/pentane, 1/1); IR (neat) 3491, 2949, 1730, 1440, 1244, 914, 734 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.19–7.05 (m, 2 H), 6.86–6.79 (m, 2 H), 4.12 (dt, J = 2.6 and 12 Hz, 1 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.47–3.34 (m, 1 H), 3.44 (s, 3 H), 3.18–2.98 (m, 1 H), 2.47–2.05 (m, 3 H), 1.97–1.83 (m, 5 H); ^{13}C NMR (50 MHz) δ 176.86, 175.01, 156.81, 133.23, 128.45, 127.54, 120.41, 110.84, 73.79, 55.22, 54.19, 51.94, 51.38, 48.04, 40.49, 39.16, 27.99, 23.60. Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.21; H, 7.21.

***rac*-(1*R*,2*S*,5*R*,6*R*)-2,5-Bis[(methyloxy)carbonyl]-6-*o*-anisylcycloheptan-1-ol (41b)**: mp 82–84 °C; R_f 0.17 (ethyl ether/pentane, 1/1); IR (neat) 3384, 2952, 1727, 1596, 1422, 1244, 881, 756 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.16 (dt, J = 1.5 and 7.5 Hz, 1 H), 7.03 (dd, J = 1.7 and 7.5 Hz, 1 H), 6.87–6.98 (m, 2 H), 4.44 (d broad, J = 6.1 Hz, 1 H), 4.15 (ddd, J = 1.8 and 6.3 Hz, 1 H), 3.81 (s, 3 H), 3.71 (s, 3 H), 3.21 (s, 3 H), 3.12 (ddd, J = 6.6, 6.4 and 3.0 Hz, 1 H), 2.97 (s broad, 1 H), 2.62 (dt, J = 10.9 and 2.9 Hz, 1 H), 2.51 (ddd, J = 13.0, 11.2 and 1.0 Hz, 1 H), 2.26–2.06 (m, 3 H), 2.01–1.83 (m, 2 H); ^{13}C NMR (50 MHz) δ 176.23, 176.07, 156.47, 133.00, 127.97, 127.16, 120.20, 110.10, 67.98, 55.43, 52.35, 51.96, 50.88, 46.66, 34.82, 30.04, 28.63, 22.78. Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.18.

***rac*-(1*S*,2*S*,5*R*,6*R*)-2,5-Bis[(methyloxy)carbonyl]-6-furylcycloheptan-1-ol (42a)**: R_f 0.33 (ethyl ether/pentane, 9/1); IR (neat) 3463, 2949, 1730, 1440, 1165, 1019 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.26 (dd, J = 0.7 and 1.75 Hz, 1 H), 6.21 (dd, J = 1.9 and 3.2 Hz, 1 H), 5.96 (d broad, J = 3.2 Hz, 1 H), 4.12 (dt, J = 3.0 and 10.1 Hz, 1 H), 3.71 (s, 3 H), 3.58 (s, 3 H), 3.37 (dt, J = 2.3 and 10.45 Hz, 1 H), 2.85–2.75 (m, 2 H), 2.50–2.39 (m, 1 H), 2.19–1.83 (m, 5 H), 1.65 (s broad, 1 H); ^{13}C NMR (50 MHz) δ 175.58, 175.54, 157.34, 141.17, 109.82, 104.16, 72.86, 53.68, 51.86, 51.71, 48.27, 38.75, 36.40, 27.36, 23.61. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.77; H, 6.82.

***rac*-(1*R*,2*S*,5*R*,6*R*)-2,5-Bis[(methyloxy)carbonyl]-6-furylcycloheptan-1-ol (42b)**: R_f 0.50 (ethyl ether/pentane, 9/1); IR (neat) 3508, 2950, 1739, 1440, 1199, 1016 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.27 (dd, J = 0.9 and 1.71 Hz, 1 H), 6.22 (dd, J = 3.2 and 1.9 Hz, 1 H), 5.96 (d broad, J = 3.3 Hz, 1 H), 4.42–4.38 (m, 1 H), 3.83–3.60 (m, 1 H); 3.70 (s, 3 H), 3.48 (s, 3 H), 3.22–3.11 (m, 2 H), 2.62–2.57 (m, 1 H), 2.29–2.21 (m, 3 H), 1.97–1.82 (m, 3 H); ^{13}C NMR (50 MHz) δ 176.35, 175.21, 157.03, 141.11, 109.97, 105.23, 68.00, 51.96, 51.47, 51.26, 47.31, 34.29, 33.98, 26.60, 24.40. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.77; H, 6.82.

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