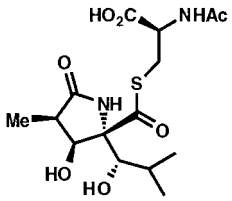
An Efficient and Concise Enantioselective Total Synthesis of Lactacystin**

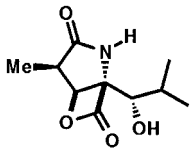
E. J. Corey,* Weidong Li, and Tohru Nagamitsu

Dedicated to Professor Satoshi Ōmura

Lactacystin (**1**), a microbial product first reported by Ōmura et al.,[1, 2] is a remarkably selective and potent inhibitor of proteasome-mediated degradation of ubiquitin-tagged proteins.[3, 4] Lactacystin and the equipotent β-lactone **2**[5] function by acylating a catalytically crucial terminal threonine residue on one of the 28 protein subunits that form



Lactacystin **1**



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the cylindrical structure of the 20*S* proteasome (Figure 1).[3, 4] This was confirmed by X-ray crystallographic studies (at 2.4 Å resolution) of the 20*S* proteasome inactivated by lactacystin.[6, 7] Another interesting finding in the X-ray studies was that the isopropyl group of lactacystin is bound in a hydrophobic pocket of the lactacystin-labeled proteasome subunit.[6] Because the proteasome system is involved in the degradation of countless proteins, including not only misfolded and denatured molecules[8] but also proteins involved in cell cycle progression[9] and regulation of gene transcription,[10] lactacystin has emerged as a very important new tool for the study of protein biochemistry and cell biology. Lactacystin prepared by the route of the first total synthesis[5, 11] has been used in numerous biological laboratories. In addition, synthetic **1** has been produced by three other multistep processes.[12–14] The continuing need for synthetic lactacystin motivated us to develop a shorter synthesis of **1** which is also amenable to the efficient preparation of structural analogues in which the isopropyl subunit of **1** is replaced by other lipophilic groups. This constraint (which dictates the introduction of the isopropyl group of **1** late in the synthesis) and the use of the γ-lactam α-carbon atom as the initiating stereocenter for the control of subsequent stereochemical elaboration led to the retrosynthetic strategy outlined in Scheme 1. In this plan BG is a blocking group with the following properties: 1) readily replaceable by hydrogen in intermediate **A**, 2) sufficiently bulky to control the stereochemistry of hydroxymethylation of β-keto ester **B** (i.e., to serve as a controller of diastereoselectivity), and 3) suitable for large-scale enantioselective synthesis of the malonic acid mono ester **C**. The full synthesis is outlined in Scheme 2.

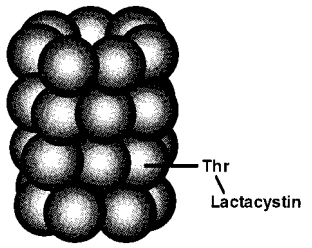
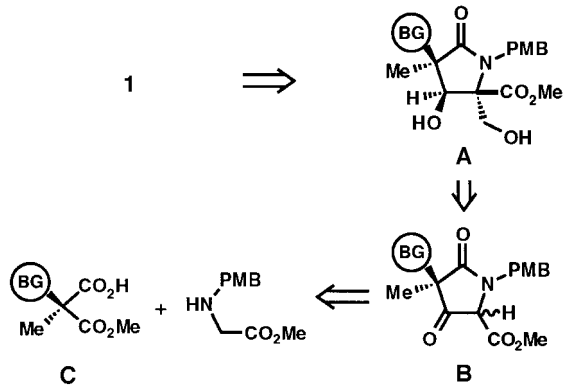


Figure 1. Schematic representation of the 20*S* proteasome after irreversible inhibition by lactacystin (**1**) or **2**.



Scheme 1. Retrosynthesis of lactacystin (**1**). PMB = *p*-methoxybenzyl.

Dimethyl methylmalonate was converted into the achiral α-methylsulfanyl derivative **3** (NaH followed by MeSCl[15] in THF, 23 °C, 12 h), which was transformed into the chiral mono ester **4** by enantioselective hydrolysis with porcine liver esterase (PLE; see Experimental Section). The crude acid (97% yield) was purified by one recrystallization of the quinine salt from aqueous ethanol to give, after acidification and extractive workup, **4** with 95% enantiomeric excess (*ee*) as a colorless oil.[16, 17] The acid chloride of **4** was coupled with methyl *N*-*p*-methoxybenzylglycinate (PMB-$NHCH_2COOMe$), and the resulting amide ester was subjected to Dieckmann cyclization to produce the keto lactam **5** as a 1:1 mixture of diastereomers (with respect to the α-carbon atom of the β-keto ester subunit).

After highly stereoselective (9:1) α-hydroxymethylation of **5** and stereospecific reduction[18] of the keto group, the crystalline dihydroxy lactam **6** [m.p. 129 °C, $[\alpha]_D^{23} = -41.8$ (c = 0.1, $CHCl_3$)] was obtained in 86% (based on **5**). The stereochemistry of **6** was established by X-ray crystallographic analysis.[19] The oily mono *tert*-butyldimethylsilyl (TBS) ether **7** was prepared from diol **6** by the following sequence: 1) selective esterification at the primary hydroxyl group by pivaloyl chloride (PivCl), 2) silylation of the secondary hydroxyl group, and 3) cleavage of the pivalate ester. Desulfurization of **7** with Raney nickel proceeded with excellent diastereoselectivity (10:1) to afford aldehyde **8** as a colorless oil in 78% yield after column chromatography and Dess–Martin periodinane oxidation.[20]

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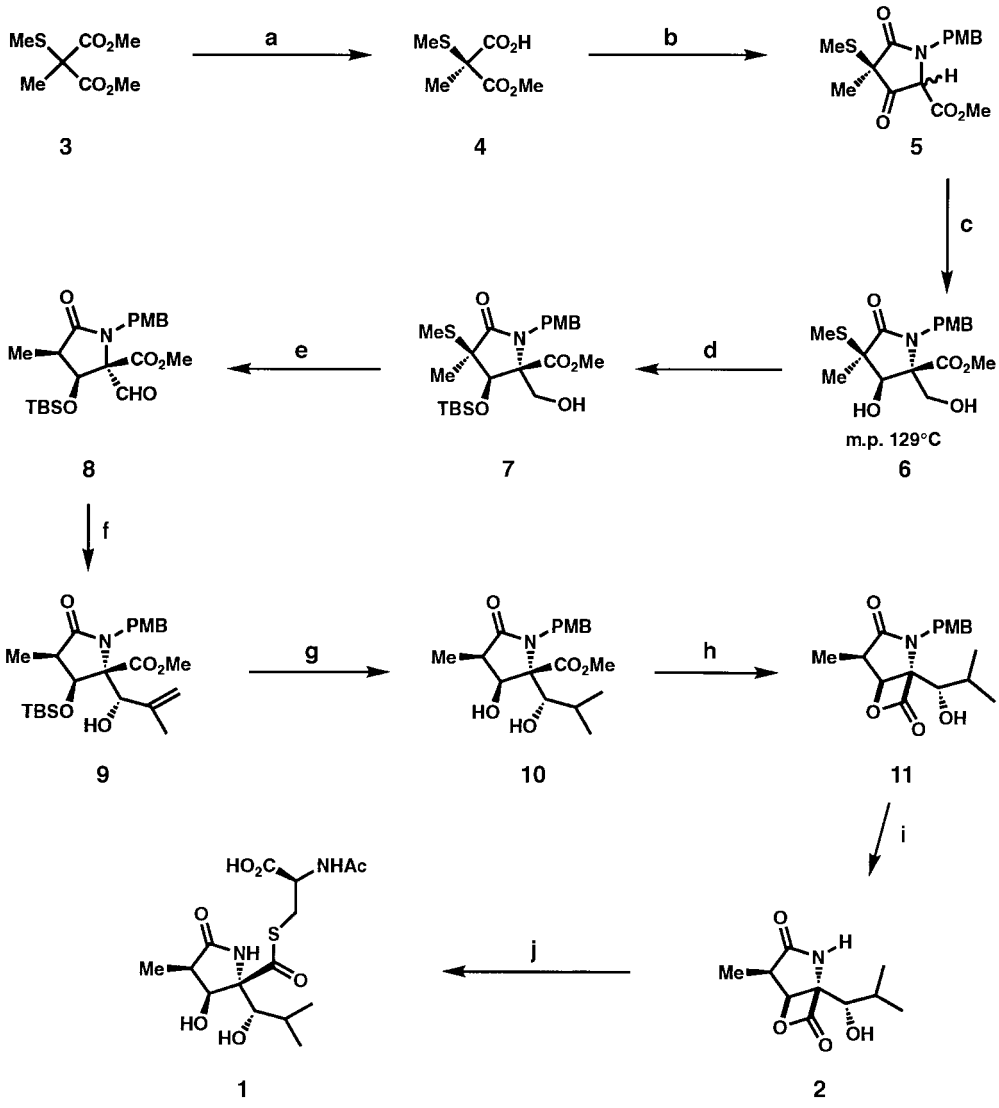

Scheme 2. Synthesis of **1**. a) 1. PLE, H_2O, pH 7.3, 23 °C, 24 h, 97 %; 2. recrystallization of the quinine salt, 62 %, 95 % *ee*; b) 1. $(COCl)_2$, DMF(cat.), 23 °C, 1 h; 2. PMB-$NHCH_2CO_2Me$, Et_3N, CH_2Cl_2, 23 °C, 1 h, 99 %; 3. LDA, THF, −78 °C, 2 h, 93 %; c) 1. DBU, THF, −78 °C, then aq. CH_2O, −78 °C, 0.5 h, 90 %; 2. $NaBH(OAc)_3$, HOAc, 23 °C, 1 h, recrystallization, 95 %, 99 % *ee*; d) 1. PivCl, pyridine, 23 °C, 10 h, 85 %; 2. TBSOTf, 2,6-lutidine, 23 °C, 12 h, 98 %; 3. NaOMe, MeOH, 23 °C, 5 h, 92 %; e) 1. Raney Ni, EtOH, 0 °C, 1 h, 82 %; 2. Dess–Martin reagent, CH_2Cl_2, 23 °C, 1 h, 95 %; f) $H_2C{=}C(Me)MgBr$, TMSCl, THF, −40 °C, 0.5 h, 97 %; g) 1. H_2/Pd–C, EtOH, 23 °C, 12 h, 99 %; 2. CF_3CO_2H/H_2O 4/1, 50 °C, 4 h, 87 %; h) 1. LiOH, THF/H_2O 1/1, 23 °C, 0.5 h; 2. BOPCl, Et_3N, CH_2Cl_2, 23 °C, 0.5 h, 90 %; i) Ce^{IV}, CH_3CN/H_2O 3/1, 23 °C, 1 h, 62 %; j) *N*-acetyl L-cysteine, Et_3N, CH_2Cl_2, 23 °C, 4 h, 99 %. LDA = lithium diisopropylamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Tf = trifluoromethylsulfanyl.

Addition of organolithium or Grignard reagents to the aldehyde **8** turned out to be problematic, since the formyl group reacted only sluggishly (probably as a consequence of steric screening) and since carbonyl addition was followed by a rapid retro-aldol cleavage reaction. However, this obstacle was overcome by the addition of the 2-propenyl Grignard reagent to a mixture of **8** and trimethylchlorosilane (TMSCl), which afforded the desired addition product **9** stereospecifically and in excellent yield after aqueous workup and isolation. Several factors contributed to the success of this process: 1) TMSCl traps the alkoxide ion resulting from the addition of the 2-propenyl Grignard reagent to the formyl group at a rate that is faster than the retro-aldol reaction; 2) at −40 °C the rate of reaction of the Grignard reagent with TMSCl is slower than that with the aldehyde **8**; 3) the TMS ether of **9** is stable under the reaction conditions, but is rapidly cleaved during aqueous work up; and 4) the stereochemistry of addition of the Grignard reagent to the formyl group of **8** is probably controlled by steric screening within a bidentate complex of Mg^{II} and the ester and formyl carbonyl groups. The reaction of isopropylmagnesium bromide with aldehyde **8** resulted in reduction of the formyl group to CH_2OH (95 % yield). Isomerically pure **9** was subjected to hydrogenation and desilylation to produce cleanly **10** [m.p. 91–92 °C, $[\alpha]_D^{23} = +12.7$ ($c = 0.06$, $CHCl_3$)]. Saponification of the ester functionality of **10** and subsequent treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 1.5 equiv) and triethylamine (3 equiv) gave the β-lactone **11** [m.p. 164 °C, $[\alpha]_D^{23} = -84$ ($c = 0.05$, $CHCl_3$)], the structure of which was fully confirmed by X-ray crystallographic analysis.[19b, 21] Cleavage of the *N*-*p*-methoxybenzyl protecting group of **11** with ceric ammonium nitrate produced the known β-lactone **2**[5] [m.p. 185 °C (decomp), $[\alpha]_D^{23} = -94$ ($c = 0.5$, CH_3CN)], which was identical with an authentic sample. Finally, treatment of **2** with *N*-acetylcysteine (1 equiv) and triethylamine (1.5 equiv) afforded pure **1** in 99 % yield; it was identical in all respects to an authentic sample of lactacystin.

The synthesis of lactacystin described here is noteworthy for a number of reasons. The synthesis is direct and simple with regard to reaction procedures and isolation of pure products. It is stereocontrolled and economical in terms of reagents. In addition, the key intermediate **8** allows access to many analogues of lactacystin in which the isopropyl group is replaced by other lipophilic residues. For example, reaction of

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8 with vinyl, allyl, and phenylmagnesium halides under the conditions described above for the conversion of **8** into **9** afforded in good yield the corresponding analogues of **9**. These compounds are of special interest in connection with the search for lactacystin analogues that exhibit species selectivity. Finally, the chiral acid ester **4** is a versatile intermediate which serves as a synthetic equivalent of configurationally unstable chiral methylmalonic acid derivatives.

Experimental Section

4: To a stirred suspension of dimethyl methylsulfanylmethylmalonate (19.0 g, 0.10 mol) in 0.1 M phosphate buffer (pH 7.3, 25 mL) and distilled water (300 mL) was added PLE (2.0 g; crude acetonic powder from *Sigma* L8251). The pH of the resulting mixture was maintained at 7.30 by regular addition of a 2 N aqueous NaOH solution with a syringe pump interfaced with a pH controller. After the mixture was stirred for 15–20 h at 23 °C, one equivalent of NaOH was consumed. The reaction mixture was treated with Celite (20 g) and filtered. The filtrate was acidified to pH 2–3 with 6 N HCl and extracted with Et_2O (3 × 300 mL), and the combined extracts were washed with brine and dried. Evaporation of the solvent in vacuo gave **4** (17.30 g, 98%, 67% *ee*) as a colorless oil, which was used for optical enrichment with quinine without further purification. A mixture of **4** (15.0 g, 0.08 mol) and quinine (27.3 g, 0.08 mol) in 50% aqueous ethanol (556 mL) was stirred at 70–80 °C for 20 min to give a clear homogeneous solution, which was cooled to 23 °C and allowed to stand for 2 d for crystallization. The resulting crystals were collected, washed with ice-cold 50% aqueous ethanol, and dried in vacuo to give a solid [m.p. 173–174 °C, $[\alpha]_D^{23} = -155$ ($c = 0.35$, 50% EtOH/H_2O)], which was dissolved in 3 N HCl (35 mL). The solution was extracted with Et_2O (3 × 300 mL), and the combined extracts were dried and concentrated in vacuo to give optically enriched **4** (7.80 g, 52%, 95% *ee*) as a colorless oil. The *ee* of **4** was determined by ^{1}H NMR spectrocopy in the presence of one equivalent of (*S*)-α-methylbenzylamine in $CDCl_3$. The mother liquor was acidified with 6 N HCl to pH 2–3 and extracted with Et_2O (3 × 300 mL). The combined extracts were dried and concentrated in vacuo to give recovered monoacid (3.75 g, < 10% *ee*), which was esterified [($COCl)_2$/PhH, DMF (cat.), 23 °C, and then MeOH] to afford **3**, which was subjected to asymmetric enzymatic hydrolysis (PLE). Purification of resulting monoacid with quinine gave additional **4** (1.8 g, total 9.6 g, 64% overall yield). $[\alpha]_D^{23} = -1.2$ ($c = 2.64$, $CHCl_3$); FT-IR (film): $\tilde{\nu} = 3134$ (br s, OH), 1731, 1713, 1260, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.73$ (s, 3H, CH_3), 2.24 (s, 3H, CH_3S), 3.83 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 14.1$, 21.4, 53.4, 55.6, 169.7, 174.8; HRMS (CI, NH_3) *m/z* calcd for $[C_6H_{14}NO_4S]^+$ 196.0644, found for $[M+NH_4]^+$ 196.0640.

Hydroxymethylation of **5:** A stirred solution of β-keto ester **5** (6.75 g, 20.0 mmol) in THF (30 mL) was treated with DBU (0.60 mL, 4 mmol) at 0 °C for 15 min, cooled to −78 °C, and treated with a solution of formalin (36 wt%, 12 M aqueous solution, 16.7 mL, 0.20 mol) in THF (10 mL). The reaction mixture was stirred for 0.5 h, quenched with 10% aqueous $CuSO_4$ solution, and extracted with Et_2O (3 × 30 mL). The Et_2O extracts were washed with brine and dried. Evaporation of the solvent in vacuo gave the crude product, which was purified by flash chromatography on silica gel to afford the desired hydroxymethylation product (6.60 g, 90%) as a colorless oil, $[\alpha]_D^{23} = +94$ ($c = 0.40$, EtOAc); FT-IR (film): $\tilde{\nu} = 3430$(br s, OH), 1740, 1697, 1513, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (dd, 1H, $J =$ 4.9, 9.1 Hz, OH), 1.55 (s, 3H, CH_3), 2.13 (s, 3H, CH_3S), 3.72 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 3.76 (dd, 1H, $J = 4.9$, 12.5 Hz, CH_2OH), 4.18 (dd, 1H, $J = 9.1$, 12.5 Hz, CH_2OH), 4.26 (d, 1H, $J = 15.2$ Hz, CH_2Ph), 5.20 (d, 1H, $J = 15.2$ Hz, CH_2Ph), 6.87, 7.34 (each d, 2H, $J = 8.6$ Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.3$, 16.8, 44.3, 53.0, 55.4, 61.9, 114.7, 126.1, 129.8, 130.5, 159.3, 165.7, 204.2; HR-MS (FAB, NBA + NaI): *m/z* calcd for $[C_{17}H_{21}NO_6SNa]^+$ 390.0987, found for $[M+Na]^+$ 390.0974.

9: A stirred solution of aldehyde **8** (100 mg, 0.230 mmol) in THF (11 mL) at −40 °C was treated sequentially with TMSCl (0.15 mL, 1.15 mmol) and isopropenylmagnesium bromide (0.5 M in THF, 1.38 mL, 0.69 mmol). After the mixture was stirred for 0.5 h at −40 °C, the reaction was quenched with saturated aqueous NH_4Cl at that temperature and stirred for an additional 0.5 h. The resulting mixture was extracted with ethyl acetate (3 × 20 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give **9** (106 mg, 97%) as colorless crystals, m.p. 153–154 °C, $[\alpha]_D^{23} = +65.7$ ($c = 0.035$, $CHCl_3$); FT-IR (film) $\tilde{\nu} = 3389$, 1698, 1683, 1514, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 0.07$ (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.82 (s, 9H, $(CH_3)_3CSi$), 1.20 (d, $J = 8.6$ Hz, 3H, 7-CH_3), 1.59 (br s, 1H, OH), 1.75 (s, 3H, $C(CH_3)=CH_2$), 2.64 (m, 1H, 7-H), 3.11 (s, 3H, CO_2CH_3), 3.78 (s, 3H, $CH_2C_6H_4OCH_3$), 3.85 (d, $J = 15.0$ Hz, 1H, $CH_2C_6H_4OCH_3$), 4.85 (d, $J = 9.2$ Hz, 1H, 6-H), 4.91 (br s, 1H, CHOH), 4.92 (d, $J = 15.0$ Hz, 1H, $CH_2C_6H_4OCH_3$), 5.12 (br s, 1H, $C(CH_3)=CH_2$), 5.20 (br s, 1H, $C(CH_3)=CH_2$), 6.81 (d, $J = 8.6$ Hz, 2H, $CH_2C_6H_4OCH_3$), 7.21 (d, $J = 8.6$ Hz, 2H, $CH_2C_6H_4OCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 178.0, 173.2, 158.9, 141.8, 130.5, 130.4, 128.9, 117.4, 113.7, 113.6, 75.2, 73.9, 69.0, 55.3, 51.7, 45.4, 40.8, 25.8, 21.2, 18.0, 11.8, −4.2, −4.6; HR-MS (FAB, NBA + NaI): *m/z* calcd for $C_{25}H_{40}NO_6Si$ 478.2625, found for $[M+H]^+$ 478.2638.

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Structure – Reactivity Relationship in the Reaction of Highly Reactive Zinc with Alkyl Bromides**

Albert Guijarro and Reuben D. Rieke*

The reaction of organic halides with magnesium or lithium in the zerovalent state is the most direct and commonly used method to prepare organometallic compounds containing these metals. However, these reactions do not show much structure selectivity. As has been stated, "the reaction of organic bromides with magnesium is among the least selective of organic reactions".[1] The formation of organolithium compounds shows great similarities to that of organomagnesium compounds.[2] In addition to these metals, zinc has become more important in recent years.[3] It tolerates a broad range of functionalities, and, since the introduction of highly reactive zinc, virtually any organozinc reagent can be prepared from the corresponding organic bromide.[4] It is generally accepted that the mechanism of these reactions is similar to those of analogous reactions of magnesium and lithium.[5] However, few mechanistic studies regarding the formation of organozinc halides are available to date.

To study the rates of reaction of alkyl bromides with highly reactive zinc, we used competitive kinetic methods.[1] The rate of reaction of organic bromides depends, in principle, on the concentration of the organic halide $[R^1Br]$ or $[R^2Br]$ and on some undefined physical characteristics of the metal surface $f(Zn)$ [Eqs. (a) and (b)]. The simultaneous determination of the concentration of two different alkyl bromides in solution that react with the same metallic surface permits a simplification to Equation (c).

$$-d[R^1Br]/dt = k_1[R^1Br]^x f(Zn) \quad (a)$$

$$-d[R^2Br]/dt = k_2[R^2Br]^x f(Zn) \quad (b)$$

$$d[R^1Br]/d[R^2Br] = k_1/k_2([R^1Br]/[R^2Br])^x \quad (c)$$

$$\ln([R^1Br]_t/[R^1Br]_0) = k_1/k_2 \ln([R^2Br]_t/[R^2Br]_0) \quad (d)$$

Assuming that $x = 1$ (that is, the reactions are first order with respect to the alkyl bromide; this is confirmed below) and integrating Equation (c) leads to Equation (d). The experimental kinetic data fit Equation (d) extremely well (Figure 1). Plots of $\ln([R^1Br]_t/[R^1Br]_0)$ versus $\ln([R^2Br]_t/[R^2Br]_0)$ are linear to greater than 95% comsumption of the most reactive halide. Evaluation of the slope by a linear regression analysis yielded k_1/k_2 directly. Every line contains between 8 and 11 points, and the linear regression coefficients are greater than 0.99 in all cases. This confirmed our

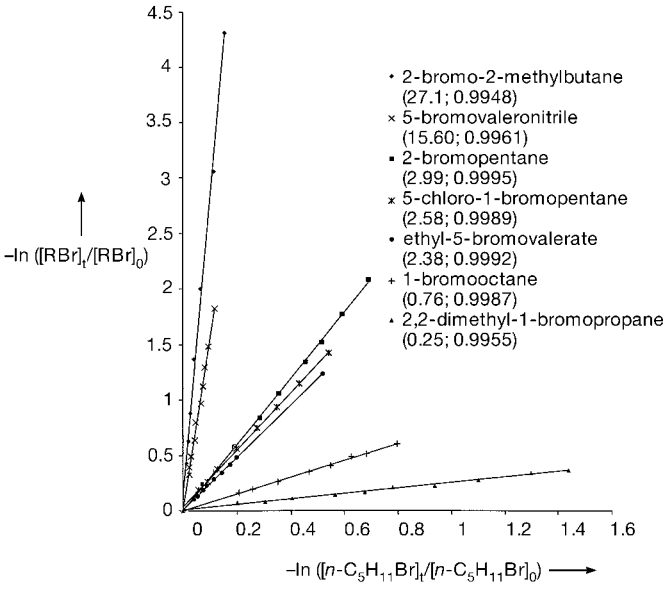

Figure 1. Experimental conformation for the validity of Equation (d) with competition reactions of 1-bromopentane and another bromoalkane with activated zinc. The ratios of the reaction rates, k_1/k_2, and the regression coefficients are given in parentheses.

hypothesis that the reaction was first order with respect to the alkyl bromide, in agreement with kinetic data reported for magnesium and lithium. Table 1 summarizes the ratio of rate constants (k_1/k_2) determined for all pairs of substrates assayed. Since the yields of organozinc bromides obtained with this procedure are very high,[4] side reactions perturb the final results only slightly.

The reaction shows selectivity with respect to the nature of the organic moiety (Table 1). The effect of the alkyl halide on the rate of the electron transfer decreases in the order tertiary > secondary > primary; the ratio of the rates is

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