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Synthesis of chiral 4,4-disubstituted-dihydropyridazines

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Abstract—In this paper, a novel general route to the stereospecific synthesis of chiral dihydropyridazines relying on the stereospecific formation of 1,4-diones is presented. The chirality is provided through the application of bicyclic lactams to the synthesis of the required diones. Treatment of the diones with hydrazine produces the pyridazine targets. In this report, the synthesis of four chiral 6-phenyl-4,4-disubstituted-1,4-dihydropyridazines is also presented.
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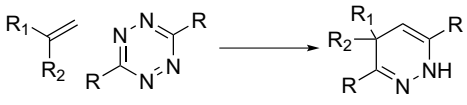
1. Introduction

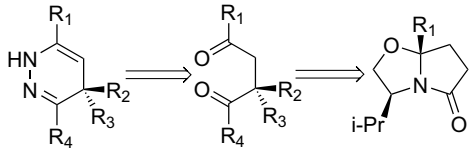
The pyridazine family of heterocycles has been known for more than a century. Testament for the diverse bioactivity displayed by pyridazine derivatives is found in the increasing number of papers and patents in the recent years.[1]

The most common approach to the synthesis of 1,4-dihydropyridazines is the 4+2 cycloaddition of a suitably substituted olefin with a tetrazine derivative through the intermediacy of the 4,5-dihydropyridazine (Scheme 1).[2] Han and Ong recently reported a nice application of tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron to control the regio- and stereoselectivity of a spirocyclic Diels–Alder product.[3] Such methods are limited in that the substituents at the 3 and 6 positions of the product are identical as they originate from the symmetrical tetrazine.



Scheme 1.

As a part of our continuing studies directed toward the asymmetric synthesis of the members of the pyridazine family, we recognized that the synthesis of suitably substituted 1,4-diketones from bicyclic lactams would allow access to chiral 4,4-disubstituted-dihydropyridazines (Scheme 2).[4]



Scheme 2.

Chiral bicyclic lactams have been demonstrated to be useful and versatile precursors for the enantioselective synthesis of a number of nitrogen heterocycles, enones, diones and ketoacid molecular structures.[5] Among the chiral non-racemic nitrogen heterocycles produced to date are the piperidines, pyrrolidines, pyrrolidinones and the tetrahydro-isoquinolines.

Phenyl, alkyl, and hydride species have previously been utilized as the bridgehead species on the bicyclic lactam. Previous conversions to diones have utilized hydrogen and alkyl lithium species to provide a route to chiral non-racemic diones.[6] We envisioned that the ability to vary these fragments would allow for the formation of pyridazines

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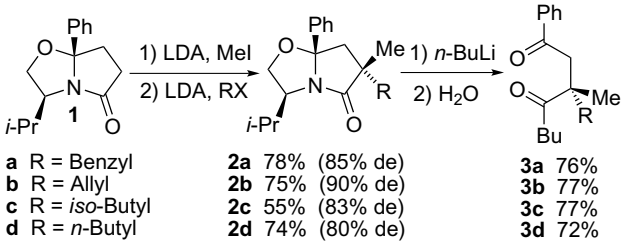
where the substituents at the 3 and 6 positions may be varied.

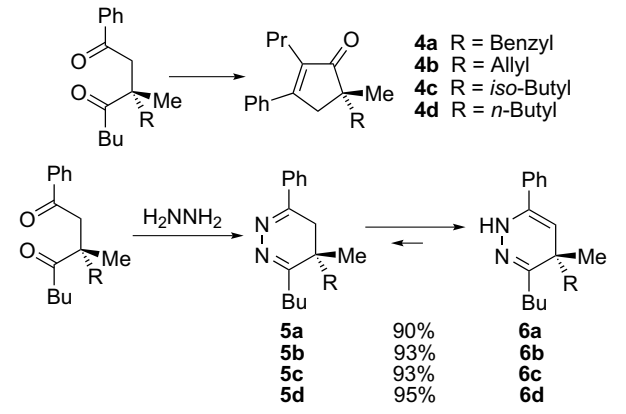
2. Results and discussion

The initial phase of the study involved the synthesis of four chiral α,α-disubstituted-γ-diketones (Scheme 3). This was achieved in a straightforward fashion via the general bicyclic lactam protocol developed by Meyers et al.[6] The disubstituted bicyclic lactams **2a**–**d** were produced in 55–78% yield from [3.3.0] bicyclic lactam **1** following chromatographic separation from the diastereomer. Treatment of the bicyclic lactam **2** with an alkyl lithium reagent allows for the production of the dione, which contains different groups at the 3- and 6-positions of the final product. In our case, *n*-butyl lithium was used to produce the desired diones **3a**–**d** after hydrolytic workup.



Scheme 3.

Diones **3** spontaneously cyclize to enones **4a**–**d** (Scheme 4). This observation has been taken advantage of previously by Meyers et al.[6] The diones may be stored in pure form under refrigeration with minimal cyclization. To avoid the formation of these self-cyclized products, the diones were submitted to reaction with hydrazine as quickly as possible to produce the target chiral 4,5-dihydropyridazines. It was anticipated that the 4,5-dihydropyridazines would rapidly and spontaneously tautomerize to the desired 1,4-dihydropyridazines. The NMR spectra of the reaction products show only resonances associated with 4,5- and 1,4-dihydropyridazines **5a**–**d** and **6a**–**d**, of which the latter predominate as over 90% of the mixture.



Scheme 4.

Analysis of the target 1,4-dihydropyridazines **5a**–**d** was complicated by their air oxidation. 4,5-Unsubstituted, monosubstituted and vicinal disubstituted dihydropyridazines form pyridazines on exposure to molecular oxygen. The geminal disubstitution in the compounds produced in this study **5a**–**d** precluded this reaction but did not prevent other oxygen induced decomposition. The formation of hydroperoxides and subsequent decomposition of dihydropyridazines has previously been proposed by Baker et al.[7] By storing the compounds under an argon atmosphere, we found them to be stable for at least six weeks.

3. Conclusion

The protocol applied demonstrates the potential to synthesize differentially substituted chiral 4,4-disubstituted-1,4-dihydropyridazines, with the advantage of being able to control the identity of the groups at all substitution positions.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. Reagents were generally the best quality commercial grade and used without further purification unless otherwise indicated. Diisopropylamine (Aldrich) was distilled and dried according to standard procedure prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl. The pH 5.0 buffer consisted of a mixture of 50 mL 0.1 M in potassium hydrogen phthalate and 22.6 mL of 0.1 M NaOH. TLC was performed using Whatman PE SIL G/UV 250 μm layer, polyester UV 254 silica gel plates. Radial chromatography was employed using 1 mm or 2 mm layer rotors with silica gel GF (ANALTECH). Column chromatography was conducted using 70–230 mesh, 60 Å silica gel. Microanalyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Optical rotations were performed on a JASCO P-1010 polarimeter. Melting points are uncorrected. IR (infrared spectra) were recorded on a Perkin–Elmer 1310 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AC-250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C) and Techmag Apollo (400 MHz for ^{1}H and 100 MHz for ^{13}C) as solutions in $CDCl_3$ (Aldrich Chemical Company; spectra grade). Chemical shifts are reported in δ unit-parts per million (ppm) downfield from tetramethyl silane (TMS) as the internal reference. Splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet, t, triplet; q, quartet.

4.2. General protocol for α-alkyl-α-methyl bicyclic lactams 2a

To an oven dried 50 mL round-bottom flask, equipped with a stirring bar and purged with nitrogen, were added THF (20 mL) and diisopropylamine (0.56 mL, 4.4 mmol). The solution was cooled to 0 °C in an ice bath and 1.9 M *n*-butyl lithium in hexane (2.52 mL, 4.8 mmol) was added

dropwise. After 5 min, the reaction temperature was lowered to −78 °C in a dry ice-*iso*-propanol bath. (3*R*,7a*R*)-Tetrahydro-6-methyl-3-(1-methylethyl)-7a-phenyl-pyrrolo-[2,1-b]oxazol-5(6*H*)-one (0.52 g, 2 mmol) in 2 mL of dry THF was added to the solution. The mixture was stirred for 2–3 h at −78 °C, and alkyl iodide (6 mmol) was added via syringe. The solution was stirred for 4–5 h at −78 °C and then the reaction was quenched with 5–10 mL saturated ammonium chloride aqueous solution. After warming to room temperature, the mixture was concentrated under vacuum and extracted with 3 × 15 mL of methylene chloride, dried over anhydrous sodium sulfate, and concentrated under vacuum. Radial or flash chromatography (1:9, ethyl acetate–hexane) gave pure product, which was used in the next step.

4.2.1. (3*S*,6*S*,7a*S*)-Tetrahydro-6-(2-propenyl)-6-methyl-3-(1-methylethyl)-7a-phenyl-pyrrolo[2,1-b]oxazol-5(6*H*)-one 2b. Yield 82%; mp 79–80 °C; IR (CCl_4 cm^{-1}) 3060, 2920, 1740, 1455, 768, 705; ^1H NMR δ 7.48 7.27 (m, 5H), 5.80–5.63 (m, 1H), 5.13–5.17 (m, 2H), 4.19 (dd, $J = 7.89$, 8.22 Hz, 1H), 3.69–3.59 (m, 1H), 3.37 (dd, $J = 7.72$, 8.36 Hz, 1H), 2.61 (d, $J = 14.15$ Hz, 1H), 2.36 (dd, $J = 6.80$, 13.73 Hz, 1H), 2.22 (dd, $J = 7.78$, 13.74 Hz, 1H), 1.94 (d, $J = 14.10$ Hz, 1H), 1.29 (s, 3H), 1.19–1.10 (m, 4H), 0.67 (d, $J = 6.07$ Hz, 3H); ^{13}C NMR δ 185.3, 143.4, 133.9, 128.6, 128.0, 125.1, 118.6, 99.6, 70.8, 63.2, 47.2, 46.3, 43.2, 32.6, 25.6, 21.0, 18.7. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.21; H, 8.42; N, 4.68. Found: C, 76.51; H, 8.53; N, 4.60.

4.2.2. (3*S*,6*S*,7a*S*)-Tetrahydro-6-methyl-3-(1-methylethyl)-6-(2-methylpropyl)-7a-phenyl-pyrrolo[2,1-b]oxazol-5(6*H*)-one 2c. Yield 60%, $[\alpha]_D^{20.7} = +6.9$ (*c* 1.5, $CHCl_3$) IR (film, cm^{-1}) 3080, 2920, 1740, 1455, 785, 730; ^1H NMR δ 7.49–7.27 (m, 5H), 4.20 (dd, $J = 7.69$, 8.42 Hz, 1H), 3.69–3.59 (m, 1H), 3.33 (dd, $J = 7.76$, 8.44 Hz, 1H), 2.66 (d, $J = 14.14$ Hz, 1H), 2.02 (d, $J = 14.06$ Hz, 1H), 1.81–1.78 (m, 1H), 1.67–1.44 (m, 2H), 1.28 (s, 3H), 1.18–1.10 (m, 4H), 0.94 (d, $J = 6.57$ Hz, 3H), 0.84 (d, $J = 6.57$ Hz, 3H), 0.67 (d, $J = 6.13$ Hz, 3H); ^{13}C NMR δ 186.1, 143.6, 128.5, 128.0, 125.1, 99.6, 70.8, 63.3, 47.3, 47.1, 46.7, 32.7, 26.7, 24.9, 21.0, 18.7. Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.14; H, 9.27; N, 4.44. Found: C, 76.25; H, 9.42; N, 4.39.

4.2.3. (3*S*,6*S*,7a*S*)-Tetrahydro-6-butyl-6-methyl-3-(1-methylethyl)-7a-phenyl-pyrrolo[2,1-b]oxazol-5(6*H*)-one 2d. Yield 80%; $[\alpha]_D^{20.6} = +4.5$ (*c* 1.7, $CHCl_3$) IR (film, cm^{-1}) 3050, 2950, 1715, 1440, 770, 705; ^1H NMR δ 7.48–7.27 (m, 5H), 4.19 (dd, $J = 7.97$, 8.13 Hz, 1H), 3.70–3.59 (m, 1H), 3.35 (dd, $J = 7.83$, 8.21 Hz, 1H), 2.56 (d, $J = 14.15$ Hz, 1H), 1.97 (d, $J = 14.14$ Hz, 1H), 1.63–1.24 (m, 9H), 1.17–1.02 (m, 4H), 0.89 (t, $J = 7.10$ Hz, 3H), 0.67 (d, $J = 6.02$ Hz, 3H); ^{13}C NMR δ 186.0, 143.6, 128.6, 128.0, 125.1, 99.5, 70.8, 63.2, 47.3, 46.7, 38.6, 32.6, 26.6, 26.1, 23.1, 21.0, 18.7, 14.0. Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.14; H, 9.27; N, 4.44. Found: C, 76.26; H, 9.44; N, 4.41.

4.3. General protocol for chiral auxiliary removal as described for 3-alkyl-3-methyl-1-phenyl-1,4-octane-diones 3

To an oven dried 50 mL round-bottom flask, equipped with a stirring bar and purged with nitrogen, 20 mL of THF and a 2 mL THF solution of dialkyl bicyclic lactam (1.0 mmol) were added and the solution cooled to −78 °C in the dry ice-isopropanol bath. Then 4.0 mmol of 1.9 M *n*-butyl lithium in hexane added. The solution was stirred for 1–1.5 h at −78 °C, quenched with 5 mL saturated ammonium chloride aqueous solution, warmed to room temperature and concentrated under vacuum. The solution was extracted with 3 × 15 mL methylene chloride. The organic phase was washed with saturated brine and dried over anhydrous sodium sulfate. Evaporation of the solution gave an oil residue, which was dissolved in 30 mL of ethanol and 30 mL of pH 5 buffer, and then heated at reflux for 24 h. The solution was concentrated under vacuum to remove the ethanol and extracted with 3 × 15 mL methylene chloride. The combined methylene chloride extracts were washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude products were purified by radial chromatography (1:9 or 1:19 ethyl acetate–hexane).

4.3.1. (3*S*)-3-Benzyl-3-methyl-1-phenyl-1,4-octanedione 3a. Yield 76%; $[\alpha]_D^{20.6} = -20.6$ (*c* 2.82, $CHCl_3$) IR (film, cm^{-1}) 3080, 3045, 2975, 1685, 1600, 1585, 1495, 755, 710. ^1H NMR δ 7.90–7.86 (m, 2H), 7.57–7.50 (m, 1H), 7.46–7.39 (m, 3H), 7.30–7.21 (m, 3H), 7.10–7.05 (m, 2H), 3.52 (d, $J = 18.11$ Hz, 1H), 3.12 (d, $J = 18.11$ Hz, 1H), 2.98 (d, $J = 12.94$ Hz, 1H), 2.88 (d, $J = 12.95$ Hz, 1H), 2.67 (ddd, $J = 6.15$, 8.56, 18.14 Hz, 1H), 2.21 (ddd, $J = 6.10$, 8.48, 18.15 Hz, 1H), 1.69–1.48 (m, 2H), 1.36–1.22 (m, 5H), 0.89 (t, $J = 7.25$ Hz, 3H); ^{13}C NMR δ 214.8, 198.1, 136.9, 133.1, 130.4, 128.5, 128.1, 128.0, 126.7, 49.3, 47.9, 45.0, 38.8, 25.5, 22.3, 21.5, 14.0. Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.94; H, 8.13. Found: C, 81.87; H, 8.18.

4.3.2. (3*S*)-3-Allyl-3-methyl-1-phenyl-1,4-octanedione 3b. Yield 77%; $[\alpha]_D^{20.6} = +36.8$ (*c* 0.7, $CHCl_3$) IR (film, cm^{-1}) 3060, 2950, 2920, 2860, 1695, 1680, 1590, 1575, 1440, 1345, 1215, 1000, 910, 750, 685, ^1H NMR δ 7.94–7.89 (m, 2H), 7.58–7.51 (m, 1H), 7.46–7.40 (m, 2H), 5.81–5.64 (m, 1H), 5.11–5.02 (m, 2H), 3.51 (d, $J = 17.99$ Hz, 1H), 3.14 (d, $J = 17.99$ Hz, 1H), 2.69 (ddd, $J = 7.28$, 7.76, 17.86 Hz, 1H), 2.50 (ddd, $J = 7.28$, 7.32, 17.87 Hz, 1H), 2.36 (d, $J = 7.47$ Hz, 2H), 1.68–1.53 (m, 2H), 1.41–1.26 (m, 5H), 0.92 (t, $J = 7.23$ Hz, 3H); ^{13}C NMR δ 214.3, 198.1, 137.1, 133.2, 133.1, 128.5, 128.0, 118.9, 48.6, 47.0, 43.2, 38.0, 25.6, 22.4, 21.7, 14.0. Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.36, H, 8.88. Found: C, 79.46; H, 9.03.

4.3.3. (3*S*)-3-Methyl-3-(2′-methylpropyl)-1-phenyl-1,4-octanedione 3c. Yield 77%; IR (film, cm^{-1}) 3075, 2975, 1685, 1600, 1585, 1450, 755, 695; ^1H NMR δ 7.94–7.90 (m, 2H), 7.57–7.50 (m, 1H), 7.47–7.40 (m, 2H), 3.55 (d, $J = 17.83$ Hz, 1H), 3.10 (d, $J = 17.83$ Hz, 1H), 2.71 (ddd, $J = 6.33$, 8.43, 17.84 Hz, 1H), 2.50 (ddd, $J = 6.44$, 8.26, 17.83 Hz, 1H), 1.76–1.46 (m, 4H), 1.41–127 (m, 5H), 0.95–0.88 (m, 9H), ^{13}C NMR δ 214.8, 198.2, 137.3, 133.0, 128.5, 127.9, 49.1, 48.7, 47.7, 37.9, 25.8, 25.0, 24.8, 24.3, 22.4, 22.1, 14.0. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.11; H, 9.78. Found: C, 79.22; H, 9.93.

4.3.4. (3*S*)-3-Butyl-3-methyl-1-phenyl-1,4-octanedione 3d. Yield 72%, IR (film, cm^{-1}) 3070, 2970, 1700, 1680, 1595,

1580, 1445, 750, 690; ^{1}H NMR δ 7.94–7.90 (m, 2H), 7.57–7.50 (m, 1H), 7.46–7.40 (m, 2H), 3.52 (d, $J = 17.84$ Hz, 1H), 3.10 (d, $J = 17.84$ Hz, 1H), 2.71 (ddd, $J = 7.27$, 7.27, 17.77 Hz, 1H), 2.48 (ddd, $J = 7.02$, 7.26, 17.76 Hz, 1H), 1.65–1.50 (m, 4H), 1.41–1.15 (m, 9H), 0.95–0.86 (m, 6H); ^{13}C NMR δ 214.8, 198.3, 137.2, 133.0, 128.5, 128.0, 48.7, 39.5, 37.8, 26.3, 25.7, 23.3, 22.4, 21.6, 14.0, 13.9. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.11; H, 9.78. Found: C, 79.07; H, 9.80.

4.4. General protocol for 4,4-disubstituted-3-butyl-6-phenyl-dihydropyridazines 5 and 6

To a 3 mL vial equipped with a stirring bar were added 3-alkyl-3-methyl-1-phenyl-1,4-octanedione (0.2 mmol) and 0.2 mL absolute ethanol. The vial was then purged with nitrogen and hydrazine monohydrate (1–1.5 mmol) was added. After being stirred at room temperature for 0.5 h, the reaction solution was refluxed for 12 h, cooled to room temperature, and concentrated under vacuum. This gave a yellow oil, which was not further purified because of its sensitivity to air. Usually, dihydropyridazines having alkyl or aryl substituents in the ring at the 3- and 6-positions exist in solution in an equilibrium between the 1,4-dihydro and 4,5-dihydro tautomers. The resonances of the 1,4-dihydropyridazine compounds predominate in the NMR spectra. The clearly observable resonance are noted below.

4.4.1. (4*S*)-4-Benzyl-3-butyl-4-methyl-6-phenyl-1,4-dihydropyridazine 6a. 90% IR (film, cm^{-1}) 3320 (br), 3060, 3025, 2960, 1595, 1450, 750, 700; ^{1}H NMR δ 7.49–7.12 (m, 1H), 4.47 (d, $J = 2.36$ Hz, 1H), 2.75 (d, $J = 12.72$ Hz, 1H), 2.61 (d, $J = 12.72$ Hz, 1H), 2.26–2.20 (m, 2H), 1.73–1.64 (m, 2H), 1.50–1.35 (m, 2H), 1.32 (s, 3H), 1.00 (t, $J = 7.25$ Hz, 3H); ^{13}C NMR δ 149.7, 139.1, 137.3, 135.2, 130.7, 128.8, 128.4, 127.6, 126.1, 125.3, 99.8, 43.0, 38.6, 31.4, 29.1, 24.5, 22.8, 14.1.

4.4.2. (4*S*)-4-Allyl-3-butyl-4-methyl-6-phenyl-1,4-dihydropyridazine 6b. 93% IR (film, cm^{-1}) 3310 (br), 3060, 2950, 1635, 1585, 1460, 755, 695; ^{1}H NMR δ 7.47–7.31 (m, 5H), 7.16 (br, 1H), 5.93–5.77 (m, 1H), 5.08–5.00 (m, 2H), 4.53–4.52 (d, $J = 2.22$ Hz, 1H), 2.31 2.20 (m, 2H), 2.15–1.95 (m, 2H), 1.67–1.53 (m, 2H), 1.50–1.31 (m, 2H), 1.22 (s, 3H), 0.95 (t, $J = 7.25$ Hz, 3H); ^{13}C NMR δ 149.5, 138.7, 135.0, 134.3, 128.6, 128.2, 125.1, 117.4, 99.9, 43.6, 37.1, 30.9, 29.1, 25.2, 22.7, 13.9.

4.4.3. (4*S*)-3-Butyl-4-methyl-4-(2′-methyl)-propyl-6-phenyl-1,4-dihydropyridazine 6c. 93% IR (film, cm^{-1}) 3310, 3050, 2940, 1650, 1595, 1455, 755, 695; ^{1}H NMR δ 7.44–7.31 (m, 5H), 6.99 (br, 1H), 4.50 (d, $J = 2.06$ Hz, 1H), 2.28–2.21 (m, 2H), 1.86–1.70 (m, 1H), 1.67–1.52 (m, 2H), 1.46–1.32 (m, 2H), 1.30–1.14 (m, 5H), 1.12–0.84 (m, 9H); ^{13}C NMR δ 150.6, 137.7, 135.5, 128.7, 128.2, 125.0, 101.5, 48.8, 37.5, 30.8, 29.3, 28.0, 25.2, 24.9, 24.2, 22.9, 14.1.

4.4.4. (4*S*)-3,4-Dibutyl-4-methyl-6-phenyl-1,4-dihydropyridazine 6d. 95% IR (film, cm^{-1}) 3310, 3050, 2950, 1650, 1595, 1455, 755, 695. ^{1}H NMR δ 7.45–7.27 (m, 5H), 7.00 (br, 1H), 4.49 (d, $J = 2.08$ Hz, 1H), 2.30–2.22 (m, 2H), 1.68–1.51 (m, 2H), 1.48 1.20 (m, 1H), 0.99–0.83 (m, 6H); ^{13}C NMR δ 153, 138.3, 135.5, 128.7, 128.3, 125.1, 40.3, 37.3, 30.8, 29.4, 27.2, 26.8, 23.3, 22.8, 14.12, 14.09.

Acknowledgments

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